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# INTRACRANIAL ANEURYSMS

## A CLINICAL AND PATHOLOGICAL STUDY OF SUBARACHNOID AND INTRACEREBRAL HAEMORRHAGE CAUSED BY BERRY ANEURYSMS

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### INTRODUCTION

This work is an analysis of the clinical manifestations and pathological findings in cases of intracranial berry aneurysms seen over the

eleven-year period from January 1928 to December 1938. As these cases illustrate the wide variety of clinical manifestations of aneurysmal haemorrhage and pressure, we are considering many aspects of the disease but wish to discuss more particularly (1) the clinical and pathological features of intracerebral haemorrhage from aneurysms and (2) the prognosis, diagnosis and treatment in cases of ruptured berry aneurysms.

For nearly a century aneurysms of cerebral arteries have been recognized and described pathologically. As early as 1866 Lebert mentioned some of the clinical manifestations. The occurrence of apoplectic attacks and pressure signs from such aneurysms was spoken of by Bartholow in 1872, Gowers, 1893, Beadles, 1907, and others. However, the diagnosis of intracranial aneurysms during life seems to have been very rare until recent years. The papers of Symonds (1923 and 1924) awakened interest in the clinical syndrome of spontaneous subarachnoid haemorrhage, which he recognized as usually being caused by rupture of aneurysms. Since then there have been many valuable contributions to our clinical knowledge of leaking aneurysms (Parker 1926, Bramwell 1934, Schmidt, 1930, Ayer 1934, and many others). The recognition of large aneurysms causing local pressure symptoms has been facilitated by X-ray (Sosman and Vogt, 1926) by angiography and by the increased frequency of intracranial operations. Albright 1929, Jefferson 1937, and McKinney, Acree and Soltz 1936 have described many of the local pressure effects and there have been several isolated case reports of large unruptured aneurysms. In spite of the voluminous literature on the whole subject of intracranial aneurysms however there remain many gaps in our knowledge of the aetiology, pathology and clinical manifestations.

### *Material Studied*

The clinical material upon which this report is based consisted of the following cases seen in the wards of the Toronto General Hospital from the years 1928-1938 inclusively. 118 cases of spontaneous subarachnoid haemorrhage, 8 cases of large unruptured aneurysm.

Of the 118 cases of spontaneous subarachnoid haemorrhage there were fifty-seven survivors and sixty-one fatal cases. In the small

group of large unruptured aneurysms there were four survivors and four fatal cases. In reviewing the cases of spontaneous subarachnoid haemorrhage clinically it was possible to determine the present status of thirty-seven of the survivors in 1938 one to ten years after their attack.

The pathological observations were made in the Division of Neuropathology of the University of Toronto under the direction of Professor E. A. Linell to whom we are greatly indebted for assistance. The pathological material consisted of thirty-three fatal cases of subarachnoid haemorrhage and four fatal large unruptured aneurysms. For completeness nine additional cases of unruptured aneurysm found incidentally at autopsy with no known symptoms during life were also studied.

#### PATHOLOGICAL OBSERVATIONS

##### *Aetiology of Spontaneous Subarachnoid Haemorrhage*

In employing the term spontaneous subarachnoid haemorrhage we wish to denote non-traumatic haemorrhage occurring primarily into the subarachnoid space. The anatomical and chemical aspects of subarachnoid haemorrhage were admirably expounded in the monograph of From 1904. He spoke of (1) cerebromeningeal haemorrhage in which a primarily intracerebral haemorrhage ruptures into the subarachnoid space, (2) primary subarachnoid haemorrhage—the bleeding originating from a vessel in the subarachnoid space and (3) meningocerebral haemorrhage—that is a primary subarachnoid haemorrhage with laceration and haemorrhage of adjacent cerebral tissue.

Here we are not dealing with cerebromeningeal haemorrhage except in the differential diagnosis. Meningocerebral haemorrhage was considered by From and by most writers since as a minor bruising and erosion of cerebral tissue. We wish to present cases in which large intracerebral haemorrhages occurred from arteries in the subarachnoid space. From made no contribution to the cause of primary subarachnoid haemorrhage. Many more recent writers have pointed out that ruptured aneurysms are the common cause of spontaneous subarachnoid haemorrhage though one frequently reads lengthy lists of causes other than aneurysm—ruptured arteriosclerotic artery, purpura, pertussis, acute infections and intoxications, syphilis, angiomas, etc.

In our experience massive spontaneous subarachnoid haemorrhage is practically always caused by rupture of an aneurysm

Our actual findings in thirty-four cases of fatal subarachnoid haemorrhage were as follows. In each of twenty-seven cases there was found a ruptured berry aneurysm. In six cases the bleeding point was not found. The other case was an arterial angioma of the cerebellum (a young man of twenty-two who had suffered three previous attacks of spontaneous subarachnoid haemorrhage). Most of the cases, then, were proven to be aneurysm and the only other demonstrable causative lesion was the angiomatous malformation. The six cases in which no bleeding point was determined deserve further consideration. It is only in the past six or seven years that a careful dissection of the arteries in search of the aneurysm has been carried out in our cases. The year by year incidence is thus of interest. In the five years, 1928-1932 there were nine fatal cases of spontaneous subarachnoid haemorrhage in five of which aneurysms were found, and in four (45%) the bleeding point was not detected. (One specimen, which had been in a museum jar for twelve years, labelled cerebral haemorrhage, was dismantled and dissected in 1938, and a ruptured aneurysm of the anterior communicating artery was found.) It is quite possible then that some other aneurysms were missed in the cases from the earlier years of this series. In the past six years, 1933-1938, autopsies were performed on twenty-four cases of primary subarachnoid haemorrhage. In twenty-two of these a ruptured aneurysm was found, and in only two (8%) was the bleeding point not discovered. In both of these the vessels appeared healthy. In one the main haemorrhage was around the anterior communicating artery, and in the other around the right middle cerebral artery. It is often very difficult to detect a small aneurysm in a mass of blood clot so that we suspect that an aneurysm remained undetected in each of these cases.

Since we have found aneurysm in 90% of cases of fatal spontaneous subarachnoid haemorrhage in which a careful examination of the vessels was made we feel justified in the assumption that practically all of our surviving cases of spontaneous subarachnoid haemorrhage are due to aneurysm. It is true that angiomatous malformations may be the aetiological vascular defect on rare occasions, but we have not verified any of the other mentioned causes, such as syphilis and arteriosclerosis.

*Pathological Types of Intracranial Aneurysms*

Three types of aneurysms of cerebral arteries are described by most authors—developmental mycotic and arteriosclerotic. In view of incomplete proof and dissident views as to aetiology these groups are not well defined. Acute mycotic aneurysms are rare occurring during the course of an acute or subacute endocarditis. They are small saccular aneurysms showing marked inflammatory changes and tending to occur on the branches of the Circle of Willis well out in the fissures or even in brain tissue. We have not encountered any such aneurysms in our series. Turnbull 1918 found an unusually high proportion of mycotic aneurysms. In his series of forty-four intracranial aneurysms fifteen were due to septic emboli (Fearnside 1916).

Arteriosclerotic aneurysms also are uncommon. Severe cerebral arteriosclerosis may produce elongated dilatations of the arteries of the Circle of Willis particularly in the basilar and internal carotid vessels. Such dilatation may be sufficiently great to warrant the term fusiform aneurysm. We have encountered two such arteriosclerotic aneurysms in the series described below.

The vast majority of intracranial aneurysms appear to be of one common type namely saccular aneurysms occurring in the angles formed by bifurcation or branching of the arteries of the Circle of Willis or in the proximal course of its branches. These have been variously termed—'congenital', 'developmental', 'miliary bifurcation' and "berry" aneurysms. We have preferred the purely descriptive term 'berry aneurysm'. This type of aneurysm with fairly constant gross and microscopic appearances may be seen in a wide range of ages though rarely in childhood and may be associated with healthy cerebral arteries or with varying degrees of cerebral arteriosclerosis. The cause of berry aneurysms will be discussed below after a consideration of our pathological findings. It is this common type of aneurysm with which we are concerned almost exclusively in this report.

There are a few other less common types of intracranial aneurysm. Traumatic arteriovenous aneurysms in the cavernous sinuses usually follow a fracture of the cranial base and give the characteristic picture of pulsating exophthalmos with a loud cephalic bruit. It is now well known that syphilis the cause of over 90% of aneurysms elsewhere in the body plays little or no part in the formation of cerebral aneurysms.

There are one or two cases in the literature, however of syphilitic aneurysms of the basilar artery. The military intracerebral aneurysms described by Charcot and Bouchard as the cause of the usual capsular haemorrhage have been discredited by Pick 1910 Ellis 1909, and others. Green 1930 also showed that such minute intracerebral aneurysms were really only false dissecting aneurysms of severely arteriosclerotic vessels. Berry aneurysms of cerebral arteries may occur in cases of coarctation of the aorta (Woltman and Shelden 1927 Baker and Shelden 1936) though we have not encountered any such cases here.

### *Pathological Examination of Intracranial Aneurysms*

*Incidence and Site* Forty cases with intracranial aneurysms examined pathologically include the twenty-seven cases of fatal haemorrhage from ruptured aneurysms four large unruptured aneurysms which had produced local pressure effects and nine cases of berry aneurysms found accidentally and with no known symptoms during life. These forty cases were encountered in 4618 autopsies an incidence of 87%. As the brain was removed in slightly less than half of these autopsies the actual incidence may be considerably higher. Various authors have found an incidence of from 5 to 15% (Fearnside 1916—44 in 5432 autopsies Osler 1930—12 in 800 Conway—43 in 6232 Turnbull 1918 in 92% of 4547 postmortem examinations of the head). The ages varied from twenty-one to eighty-nine with an average of fifty years. There were eighteen males and twenty-two females.

The aneurysm occurred singly in thirty cases. In each of seven cases there were two aneurysms and there were three cases which showed three aneurysms. Thus there were altogether fifty-three aneurysms in the forty cases. Two of these were arteriosclerotic fusiform aneurysms of the basilar artery (Fig 1). The remainder were berry aneurysms and occurred at the various angles of bifurcation of the vessels of the Circle of Willis or nearby in their main branches.

There were sixteen aneurysms of the middle cerebral artery in the Sylvian fissure at its first or second branching. Thirteen aneurysms were attached to the angles between the anterior cerebral and anterior



FIG. 1. ARTERIOSCLEROTIC ANEURYSM OF THE BASILAR ARTERY.

The vessel is elongated and tortuous and shows two distinct dilatations. Numerous atherosclerotic plaques are seen. A woman aged 57 with chronic nephritis and hypertension. Death caused by thrombosis of the basilar artery.



communicating arteries (One included here was formed in an anomalous reduplication of one anterior cerebral artery) The next most common site was in the region of bifurcation of the internal carotid artery where there were eleven aneurysms This area includes the various junctions of the carotid, middle and anterior cerebral and posterior communicating arteries The remaining aneurysms were in relation to the following arteries basilar, six, vertebral, three, posterior cerebral, two, and carotid, before its bifurcation, two This distribution of the aneurysms is shown more clearly in the diagram

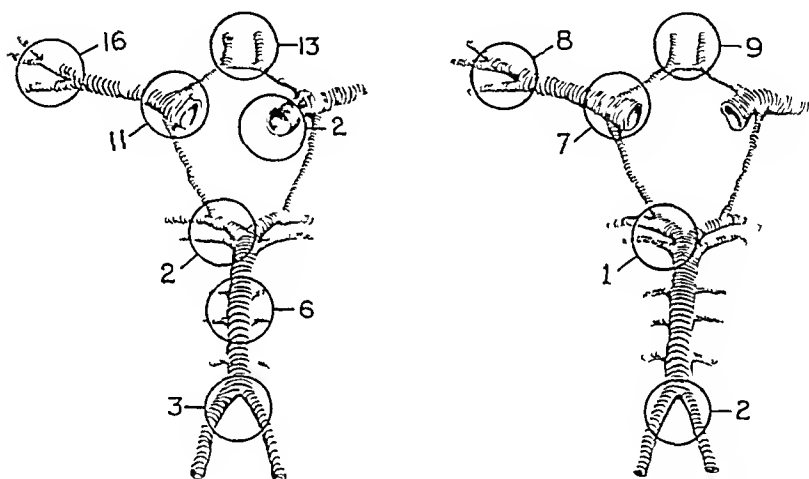


FIG 2 DRAWINGS SHOWING THE LOCATION OF FIFTY-THREE ANEURYSMS FOUND AT POST MORTEM EXAMINATION

A (Left) Total series fifty-three ruptured and unruptured aneurysms

B (Right) Twenty-seven ruptured aneurysms, the majority situated on the anterior part of the Circle of Willis

(Fig 2 A) The twenty-seven aneurysms which had ruptured were distinctly more numerous around the anterior part of the Circle of Willis as shown in Fig 2 B

The regional incidence in our series is much the same as has been found by various other writers—Gull 1859 Gowers, 1893 Beadles, 1907, Schmidt, 1930 etc Three of the four large unruptured aneurysms which presented themselves clinically with tumour symptoms, were situated on the basilar artery or at its junction with the vertebral arteries

*Gross Appearance of Aneurysms* The size of the aneurysms in the present series varied between the two extremes of a minute sac three millimeters in diameter and a large dumb-bell shaped aneurysm five centimeters in diameter. The greater number were from four to ten millimeters in size and were evenly rounded, oval or coarsely lobulated and were attached to the artery at its point of bifurcation by a short small neck. The wall of the sac, in most instances, was thin and smooth resembling the basal arteries. In some cases the aneurysm sac was nodular and whitish due to arteriosclerotic thickening. The aneurysmal sac sometimes contained fluid blood but very often was almost entirely filled by firm thrombus. Complete thrombosis of the aneurysm was particularly common in the larger ones. The aneurysm usually lay free in the subarachnoid space but in several cases was partly imbedded in the adjoining cerebral tissue. This was particularly the case with anterior communicating aneurysms impinging on the medial surface of the frontal lobe, middle cerebral aneurysms in the Sylvian fissure and the aneurysms at the carotid bifurcation which tended to indent the adjoining hippocampal uncus. This compression and erosion of neighbouring tissue is a feature of importance in regard to intracerebral leakage and will be mentioned again in that regard. Aneurysms in relation to the large basal cisterns from the basilar, vertebral and posterior cerebral arteries are less liable to become nested in the cerebral tissues. Pressure upon and adhesions with cranial nerves were seen in several cases which will be described further in the case reports.

The cerebral arteries appeared to be healthy in eight cases. In eighteen cases there was mild patchy arteriosclerosis and in the remaining fourteen cases there was severe arteriosclerosis. In two of the cases with severe cerebral arteriosclerosis, there were fusiform arteriosclerotic dilatations of the basilar artery, in the others the aneurysms were of the same saccular type as seen in the cases with no arteriosclerosis. We think it probable that the aetiology of the berry aneurysms was a common one and that arteriosclerosis was not the essential cause but probably only coincidental.

*Microscopic Appearance of Aneurysms* Microscopic examination of the aneurysm sac was carried out in approximately half of the cases. The usual finding, and that which is generally described, was a wall

composed entirely of fibrous tissue from the intima and adventitia of the parent vessels with no evidence of media or elastic tissue. In a few cases sectioned to include the neck of the sac, it was possible to show either an abrupt disappearance of the internal elastica and media, or a gradual thinning out of those layers in the aneurysm wall (Fig 3). In most cases the intima of the aneurysm showed irregular, nodular fibrous and atheromatous thickening. In some cases linear streaks



FIG 3 SECTION THROUGH THE NECK OF A BERRY ANEURYSM

On the left is the parent vessel with adventitia, media, elastica and slightly thickened intima. The media and elastica end abruptly in the neck of the aneurysm. The aneurysm wall to the right consists of a fibrous adventitia and much thickened intima. Male, aged 80. Weigert's elastic tissue stain + H & E.  $\times 30$ .

of granular calcareous material could be seen in the deeper intima. Minute extravasations of red blood cells and of phagocytosed blood pigment were frequently seen in the aneurysm walls. Frequently there were seen small rounded or linear foci of inflammatory cells amongst the fibrous tissue of the walls. These cells consisting chiefly of lymphocytes with a few plasma cells and monocytes, and occasionally some polymorphonuclear leucocytes (Fig 4) were usually seen

near the outer margin of the aneurysm wall. This patchy inflammatory reaction was in no case sufficiently marked to suggest an infective aetiology of the aneurysm but is a finding of some interest. The round cell infiltration was usually not accompanied by fresh or old haemorrhage. It seems likely that this reaction is purely a secondary or symptomatic inflammation but its exact cause is obscure. Whether it is a reaction to haemorrhage into the aneurysmal wall or to stretch-

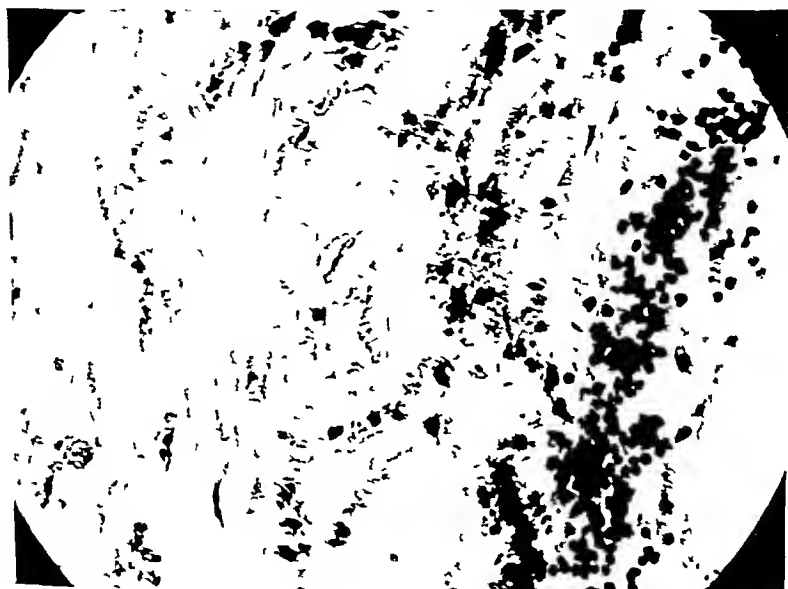


FIG. 4. HIGH POWER VIEW OF WALL OF LARGE UNRUPTURED ANEURYSM OF BASILAR ARTERY.

The wall is fibrous with adventitia to the right. There is a dense infiltration of lymphocytes and plasma cells in the outer adventitia. (Case 9 F.T.) H & E  $\times 140$

ing and tearing of the fibrous tissue we are unable to say. In one case there was evident considerable fibroblastic proliferation along with round cell infiltration.

The frequent finding of small haemorrhages in the aneurysm walls suggests that aneurysmal leakage and subarachnoid haemorrhage might occur by a gradual dissecting process without necessarily sudden violent elevation of blood pressure. This is in keeping with our observation that relatively few of the patients suffered the onset of

symptoms during strenuous exercise. The presence of mild arteritis and periarteritis probably explains the adherence to cranial nerves. In two of our cases the third nerve was imbedded in the wall of a carotid aneurysm. The occasional occurrence of a sudden third nerve paralysis without clinical evidence of haemorrhage, might be due to a local neuritis in association with such an arteritis. Such suggestions however, are purely speculative and it cannot be stated that our pathological findings really prove any other explanation of symptoms than pressure and haemorrhage.

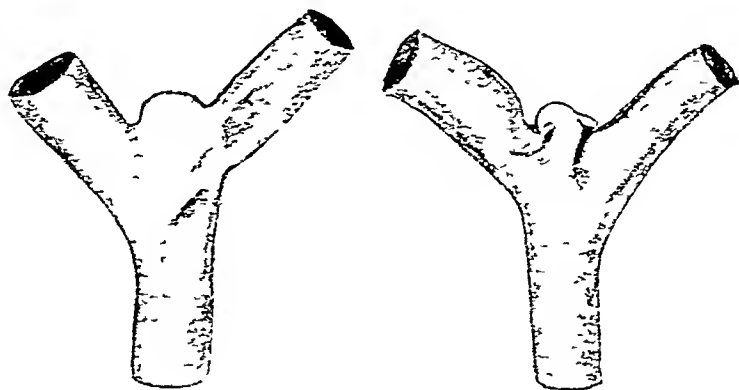


FIG 5 PENCIL SKETCH OF MINUTE ANEURYSM OF THE MIDDLE CEREBRAL ARTERY AS SEEN WITH THE DISSECTING MICROSCOPE

It is in the form of a transverse ridge across the bifurcation with a bulbous enlargement at the upper surface (left drawing). Some gross arteriosclerotic thickening is shown.

Two cases of unusually small unruptured berry aneurysms warrant further mention. One of these was at the first branching of a middle cerebral artery and the other was at the angle between the posterior cerebral and posterior communicating arteries. Each was a minute outpouching of about 2 mm in diameter and might be considered a very early stage of aneurysm formation. The middle cerebral aneurysm is shown in Fig 5 as it appeared under the dissecting microscope.

It has a linear ridge-like shape, bulbous and rounded towards the lower part of the bifurcation. A whitish, thickened arteriosclerotic patch was present in one small area. Serial sections showed the media

and internal elastic lamina to disappear at the margin of the aneurysm. The wall of the aneurysm was made up of thickened cellular and fibrous intima surrounded by a thin adventitia (Fig 6). The thickened intima had the appearance of the common arteriosclerotic endarteritis. One is tempted to assume that a degenerative process in the media in relation to the arteriosclerotic intimal thickening might have been the pathogenesis in this case. Such an aetiology of berry aneurysms



FIG 6 SECTION THROUGH ANEURYSM SHOWN IN FIGURE 5

The media and elastic tissue disappear at the neck and the wall of the sac is composed of adventitia and greatly thickened intima. Weigert's elastic tissue stain — H & E  $\times 10$

has been suggested by Tuthill. However, it is impossible to refute the possibility that the intimal thickening may have been secondary to a weakening of the media due to congenital defect. We do not feel that any conclusions can be drawn from examination of this aneurysm, but it does show very clearly the structure of a berry aneurysm at an early stage.

The second minute aneurysm had quite a different structure. Its wall was the same as that of a normal artery in that all coats, media

elastica, intima and adventitia were clearly present (Fig 7) It was found as a second aneurysm in a case in which fatal haemorrhage occurred from rupture of an aneurysm of the anterior communicating artery In this case there must have occurred a weakening, stretching and outpouching of the whole wall but certainly not a congenital absence of media This is the only aneurysm in which we have found

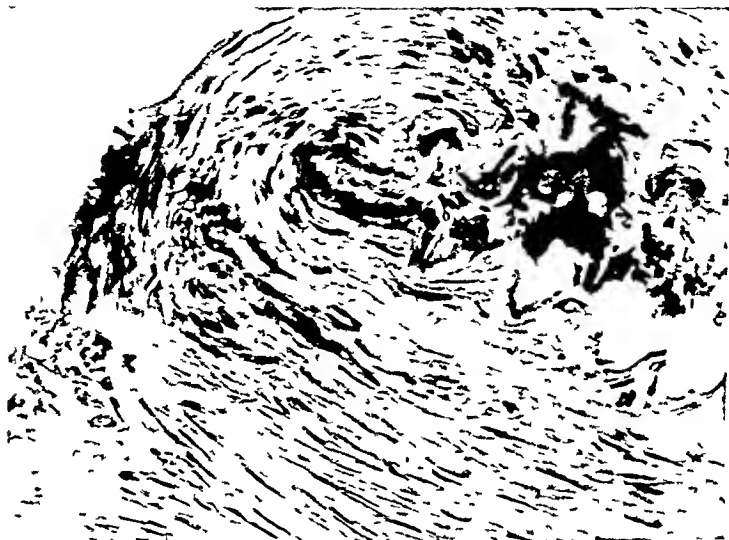


FIG 7 SECTION THROUGH THE SAC OF A SMALL UNRUPTURED ANEURYSM OF THE POSTERIOR COMMUNICATING ARTERY IN A WOMAN, AGED 49, WHO DIED FROM RUPTURE OF A LARGER ANEURYSM OF THE ANTERIOR COMMUNICATING ARTERY

The wall of the aneurysm shown here is unusual in that it contains normal media and elastica H & E  $\times 18$

an intact media and elastica and it is probably of the same type as described by Busse (1921) and termed "dehnungs aneurysmen"

#### *Aetiology of Berry Aneurysms*

The cause of berry aneurysms is not entirely clear though there is strong evidence for the existence of developmental imperfections of cerebral arteries, which probably play some part in the formation of aneurysms

Eppinger (1887) suggested that basal cerebral aneurysms were congenital, caused by defects in elastic tissue Turnbull (1918) and

more recently Forbus (1931) demonstrated the presence of local defects of the media of cerebral arteries at the apices of the angles formed by arterial branching or bifurcation. Forbus' detailed histological study of arterial bifurcations is the most exhaustive published work on this subject. He found local areas in which the media was completely absent in the cerebral arteries of each of twelve cases in which berry aneurysms were present. Moreover he found similar medial defects in the cerebral arteries of twenty-five out of thirty-three cases without berry aneurysms. The positive cases in this group included as many children as adults and medial defects were found in one of two stillborn infants examined. Arteries elsewhere in the body were studied in smaller numbers and defects were found at bifurcations in two of nine coronary arteries and in two of nine mesenteric arteries. Forbus also performed experiments by measuring fluid pressures in glass models whereby he showed that sudden increases in pressure were greatest at the points corresponding with bifurcation angles in arteries. The occurrence of medial defects at cerebral artery bifurcations in cases of berry aneurysms has been confirmed by other workers more recently (Strauss et al. 1932, Schmidt, 1930). The case reported by Nevin and Williams (1937) is of special interest. Death caused by peritoneal haemorrhage was found to have been the result of a saccular aneurysm of the splenic artery and in the same case berry aneurysms of cerebral arteries were present. Medial defects were found at bifurcations in both cerebral and splenic arteries.

We have not as yet carried out a detailed study of arterial bifurcations but have examined cerebral arteries in a small number of cases. On the basis of these examinations we are convinced that medial defects do occur. The material consisted of eight cases in one of which death occurred from a ruptured berry aneurysm of the anterior communicating artery. In seven cases no aneurysms were found macroscopically. The ages were fifteen, twenty-one, thirty-eight, forty-three, sixty-four, sixty-seven, seventy-one and seventy-two years. In each case either the basilar artery at its bifurcation or the middle cerebral artery at its first branch was examined. Longitudinal serial sections were made with paraffin embedding and stained by haematoxylin and eosin, and elastic tissue stains. In five of these eight arteries well-defined medial defects were seen (ages twenty-one



elastica intima and adventitia were clearly present (Fig 7) It was found as a second aneurysm in a case in which fatal haemorrhage occurred from rupture of an aneurysm of the anterior communicating artery In this case there must have occurred a weakening, stretching and outpouching of the whole wall but certainly not a congenital absence of media This is the only aneurysm in which we have found

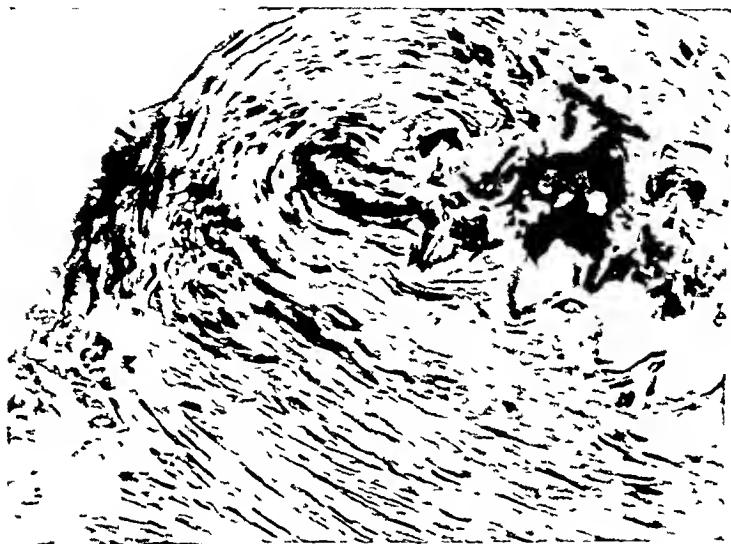


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exhibited some thinning and fragmentation of the elastica (Fig. 9); in the other the elastica appeared intact (Fig. 10). Thus we have found medial defects in four of seven cerebral arteries in cases without aneurysms, and also in the one case examined where there was a



FIG. 9 Absence of Media and Elastic Arteriosclerotic Regulation in the Artery at First Examination of an Age-Related Normal Middle Cerebral Artery.

The elastic tissue is thin and fragmented in the defective area. Weigert's elastic reaction — H. & E. — 120X.

ruptured berry aneurysm. These figures are, of course, too small to be of any statistical value.

Tatum (1933) favoured an arteriosclerotic lesion as the cause of berry aneurysms. He postulated a focal fatty degeneration of the media in association with elastic tissue changes. Strauss and Schmidt also favoured arteriosclerosis as the commonest cause of aneurysms.

thirty-eight, forty-three, seventy-one and seventy-two) They consisted of small gaps in the media at the centre of the bifurcation angles (Fig 8) At these points the wall was thin consisting only of intima, elastica and adventitia The muscle on either side appeared normal and there was no evidence of necrosis, inflammatory reaction, or

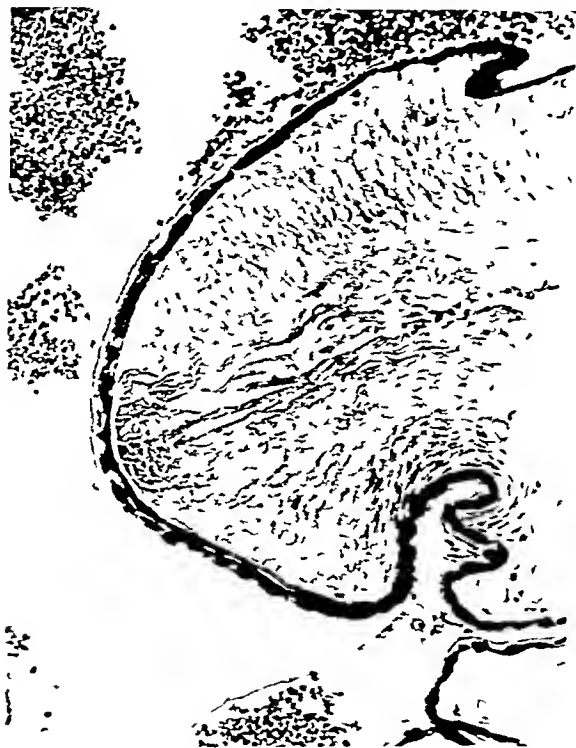


FIG 8 MEDIAL DEFECT AT THE POINT OF BIFURCATION OF AN APPARENTLY NORMAL CEREBRAL ARTERY

Media is absent in a small area at the apex of the angle The elastica is intact Weigert's elastic tissue stain + H & E  $\times 120$

scarring The elastica appeared normal and intact opposite the defect in three of the five cases Opposite one defect (a girl twenty-one years of age who died from a ruptured aneurysm), the elastica showed a marked local splitting and widening In two of the defects there were minute saccular outpouchings One of these microscopic aneu-



In criticism of Forbus' findings, Tuthill claimed that the medial defects at bifurcations could be caused by artefact due to a twisting of the tissues or a folding of the media under the elastica. In our cases we fail to see any possible artefact causing the medial defects and we

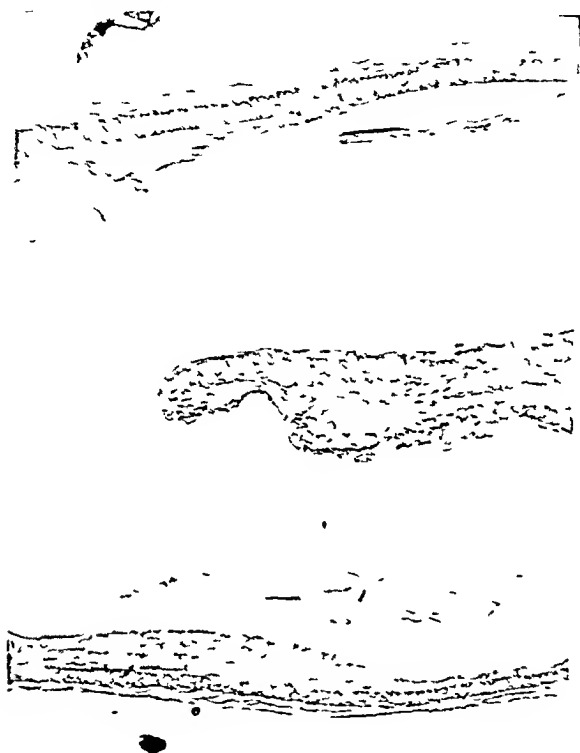


FIG 10 MEDIAL DEFECT AND MICROSCOPIC ANEURYSM IN CEREBRAL ARTERIAL BIFURCATION

To the left is the trunk of the middle cerebral artery, to the right, its first branching. In the acute angle in the centre the wall is thin due to absence of media, and there is an early pouching. H & E  $\times 40$

consider that the defects are true lesions probably developmental in origin.

From the data at hand it seems reasonable to conclude that medial defects occur at bifurcations in cerebral arteries and as berry aneurysms occur at those points, that the defects play a part in their formation. It remains possible that such defects are the whole explanation

of aneurysms it is conceivable that a large defect might become stretched by continued pressure into a saccular aneurysm. Yet there are certain difficulties in accepting defects of media as the sole factor and the following facts must be considered in forming an opinion: (1) Medial defects are often present in cerebral arteries of persons without aneurysms. (2) Berry aneurysms are rare in infancy and uncommon before adolescence. (3) Berry aneurysms are rare in arteries other than cerebral arteries though medial defects have been found in these other arteries. (4) Berry aneurysms are more commonly single than multiple.

It is our impression that structural biturcation defects in the media of cerebral arteries predispose to and determine the site of berry aneurysms but that there is another superadded, acquired lesion. The added condition apparently acts by weakening the elastica in the areas of medial defect, but we can supply no information as to the nature of this suggested lesion. The frequent finding of berry aneurysms in association with thin healthy-looking cerebral arteries suggests that the ordinary type of cerebral arteriosclerosis is not a causative factor. It is conceivable that a local arteriosclerotic process with splitting of the elastica could occur at the points of medial defect, but our very limited study of biturcation defects showed an elastic tissue degeneration in only one out of five cases. Could it be that there is some toxic or metabolic process weakening elastic tissue in these cases? If it were merely increased intravascular pressure causing the outpouching, one would expect berry aneurysms to be a much more common sequel in cases of arterial hypertension. It is probably wisest at present to accept the fact that the full aetiology of berry aneurysms is not known.

#### *Aneurysmal Haemorrhage with Particular Reference to Intracerebral Rupture*

In all of our cases of ruptured aneurysms with fatal haemorrhage, it was possible to find a gaping, ragged hole in the sac usually of quite large size. In one case, as above mentioned, the whole sac had torn off, leaving only a small torn neck. With these large tears the fatality is readily understandable and it is difficult to see how such ruptures could ever become closed and healed. The presence of

In criticism of Forbus' findings, Tuthill claimed that the medial defects at bifurcations could be caused by artefact due to a twisting of the tissues or a folding of the media under the elastica. In our cases we fail to see any possible artefact causing the medial defects and we

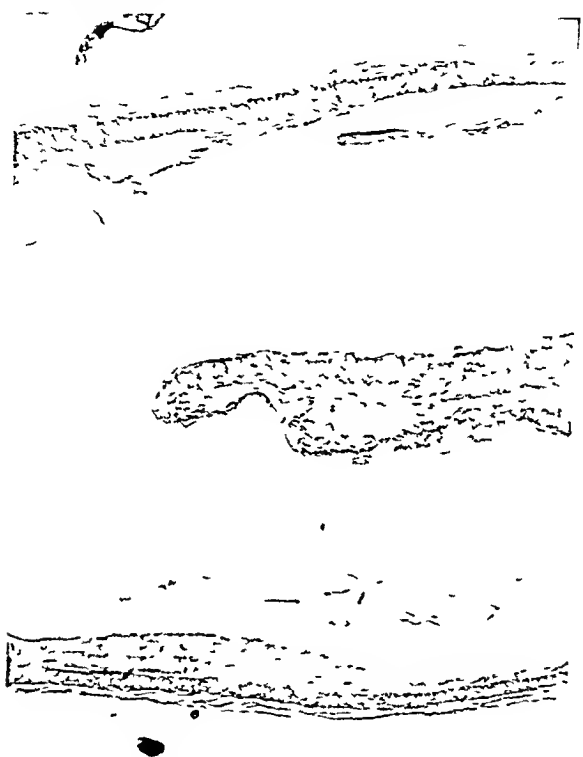


FIG 10 MEDIAL DEFECT AND MICROSCOPIC ANEURYSM IN CEREBRAL ARTERIAL BIFURCATION

To the left is the trunk of the middle cerebral artery, to the right, its first branching. In the acute angle in the centre the wall is thin due to absence of media, and there is an early pouching. H & E  $\times 40$

consider that the defects are true lesions, probably developmental in origin.

From the data at hand it seems reasonable to conclude that medial defects occur at bifurcations in cerebral arteries and as berry aneurysms occur at those points, that the defects play a part in their formation. It remains possible that such defects are the whole explanation

of aneurysms it is conceivable that a large defect might become stretched by continued pressure into a saccular aneurysm. Yet there are certain difficulties in accepting defects of media as the sole factor and the following facts must be considered in forming an opinion. (1) Medial defects are often present in cerebral arteries of persons without aneurysms. (2) Berry aneurysms are rare in infancy and uncommon before adolescence. (3) Berry aneurysms are rare in arteries other than cerebral arteries though medial defects have been found in these other arteries. (4) Berry aneurysms are more commonly single than multiple.

It is our impression that structural bifurcation defects in the media of cerebral arteries predispose to and determine the site of berry aneurysms but that there is another superadded acquired lesion. The added condition apparently acts by weakening the elastica in the areas of medial defect but we can supply no information as to the nature of this suggested lesion. The frequent finding of berry aneurysms in association with thin healthy-looking cerebral arteries suggests that the ordinary type of cerebral arteriosclerosis is not a causative factor. It is conceivable that a local arteriosclerotic process with splitting of the elastica could occur at the points of medial defect, but our very limited study of bifurcation defects showed an elastic tissue degeneration in only one out of five cases. Could it be that there is some toxic or metabolic process weakening elastic tissue in these cases? If it were merely increased intravascular pressure causing the outpouching one would expect berry aneurysms to be a much more common sequel in cases of arterial hypertension. It is probably wisest at present to accept the fact that the full aetiology of berry aneurysms is not known.

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firm thrombus in the sac could perhaps reduce the force of the bleeding and minimize the danger. It does seem likely however that most of the non-fatal cases of leaking aneurysms are due to smaller ruptures than are usually seen in these fatal cases. We have mentioned the frequent finding of small haemorrhages in the aneurysm wall and such haemorrhage might by a dissecting process produce small leakages.

Because of the situation of berry aneurysms in the Circle of Willis, or nearby on its main branches haemorrhage from a ruptured aneurysm tends to be chiefly in the subarachnoid space. In a fatal case one usually finds a massive collection of blood in the basal subarachnoid cisterns spreading out in the large fissures towards the lateral surfaces of the hemispheres. However, as pointed out by Collier the bleeding may not be entirely subarachnoid but may also be subdural, transdural, intracerebral, intraventricular or into the subarachnoid space. Courville and Olsen 1938, in a recent report, described the frequent occurrence of intracerebral haemorrhage into the frontal lobes from ruptured anterior communicating aneurysms. Such haemorrhage occurs into one or both frontal lobes, stripping up the white matter in the region of the forceps minor. Courville found it impossible to correlate these intracerebral haemorrhages with any distinct clinical syndrome. Albright mentions the occurrence of crossed hemiplegia in cases of aneurysm of the internal carotid artery but does not mention intracerebral haemorrhage as the cause. In the massive literature on the clinical and pathological features of aneurysmal haemorrhage attention has been devoted almost exclusively to subarachnoid haemorrhage and involvement of cranial nerves. True hemiplegic, aphasic, convulsive and psychotic forms of spontaneous subarachnoid haemorrhage have been mentioned but there has been no detailed consideration of the location, mechanisms and clinical syndromes due to intracerebral haemorrhage from aneurysms. We have been impressed with the frequency of signs of intracerebral haemorrhage in reviewing our cases clinically and have been fortunate in obtaining pathological verifications in several such cases. An analysis of the pathological findings shows a surprisingly great frequency of intracerebral haemorrhage. In the twenty-seven cases of ruptured aneurysms subarachnoid haemorrhage of varying degree

occurred in all. Haemorrhage was confined to the subarachnoid space in only eight cases. Intracerebral as well as subarachnoid haemorrhage occurred in nineteen cases.

We are including in the group with intracerebral haemorrhage, only well defined large haemorrhages and not merely slight bruising and erosion of cortex. The intracerebral haemorrhages were in two positions primarily, frontal and temporal and were all caused by aneu-



FIG 11 TRANSVERSE SECTION THROUGH MIDDLE OF CEREBRAL HEMISPHERES IN A CASE OF FATAL ANEURYSMAL HAEMORRHAGE

The excavation in the inferior surface of the left temporal lobe is the bed of an aneurysm at the carotid bifurcation. The aneurysm has been removed. Haemorrhage has spread upwards into the temporoparietal white matter and internal capsule.

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FIG. 13. FRONTAL LOBE. HAEMORRHAGE FROM MIDDLE CEREBRAL ANEURYSM

A (Left) Shows the base of the brain with the Sylvian fissure and massive subarachnoid haemorrhage  
B (Right) Shows the massive haemorrhage in frontal lobe white matter

haemorrhage, in five cases the bleeding into brain tissue was much larger and in three cases the subarachnoid haemorrhage was of only a negligible amount. In the drawing, the two most common positions of such intracerebral haemorrhages are indicated (Fig 12). With massive fatal ruptures the intracerebral haemorrhage in a few cases

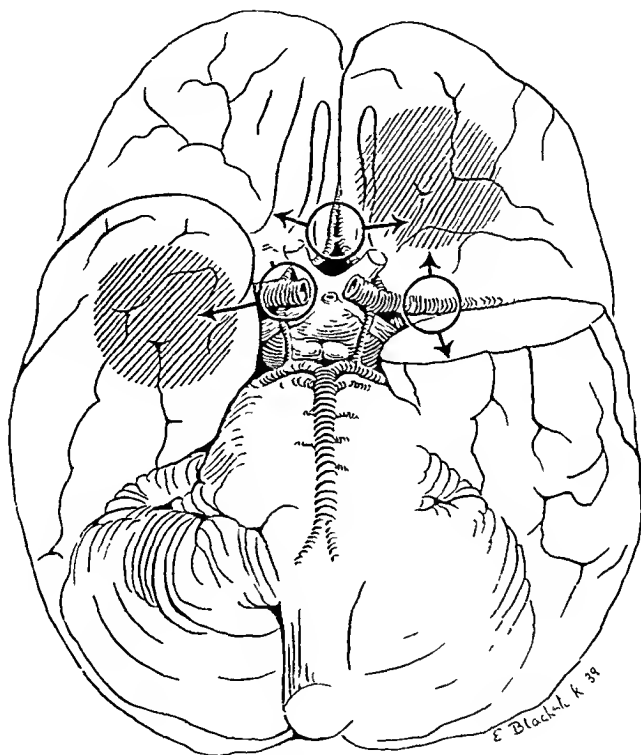


FIG 12 INTRACEREBRAL HAEMORRHAGE FROM ANEURYSMS FROM THE CIRCLE OF WILLIS

The dark circles indicate the three sites of aneurysm which commonly rupture intracerebrally. The shaded areas indicate roughly the commonest sites of such intracerebral haemorrhages.

was much less circumscribed and in one case occupied the white matter of a whole cerebral hemisphere from frontal to occipital lobe external to the lateral ventricle. The frontal lobe is much more commonly penetrated via its medial surface by anterior cerebral and communicating aneurysms and such haemorrhages are usually seen to be confined



FIG 13. FRONTAL LOBE. HAEMORRHAGE FROM MIDDLE CEREBRAL ANEURYSM

A (Left) Shows the base of the brain with the large aneurysm in the Sylvian fissure and massive subarachnoid hemorrhage  
 B (Right) Shows the massive haemorrhage in frontal lobe matter



to one or both frontal lobes. Aneurysms arising at the bifurcation of the internal carotid may readily rupture into cerebral tissue and usually gain entry by the medial surface of the hippocampal uncus. The haemorrhages in these cases may remain confined to the temporal lobe, but can readily invade laterally into the internal capsule and basal ganglia. Less commonly the carotid aneurysms may burrow through the inferior surface of the frontal lobe lateral to the optic chiasm—causing haemorrhage into the frontal or frontoparietal white matter. Aneurysms of the middle cerebral artery in the Sylvian fissure may rupture in various directions involving frontal (Fig 13), parietal or temporal regions, in our cases downward rupture into temporal lobe tissue was most common. The clinical correlation of these haemorrhages will be discussed later.

The actual number and origin of intracerebral haemorrhages from aneurysms, in our postmortem cases, was as follows. Frontal Lobe Haemorrhage—ten cases (right, five, left, three, bilateral, two) from anterior communicating aneurysms, seven, from middle cerebral aneurysms, in Sylvian fissure, two, from carotid bifurcation aneurysm, one. Temporal Lobe Haemorrhage—nine cases from middle cerebral aneurysms, in Sylvian fissure, five, from carotid bifurcation aneurysms, four.

#### *Incidence of Spontaneous Subarachnoid Haemorrhage in Comparison with Intracerebral Haemorrhage*

As stated above, there were 118 clinical cases of spontaneous subarachnoid haemorrhage in the eleven-year period, 1928–1938, and we believe that, with possibly a few exceptions, these were all due to ruptured intracranial aneurysms. In these 118 cases, there were sixty-one fatalities, a mortality rate of 52%. Postmortem examination was done in thirty-three cases.

In order to compare the incidence, age and mortality, we have determined, from the clinical and pathological records, the number of cases of intracerebral haemorrhage due to arteriosclerosis with or without hypertension during the same period (Table 1). There are, of course, difficulties and possible errors in determining the incidence of cerebral haemorrhage from clinical cases without postmortem verification. In reviewing the histories of cases diagnosed as cerebral

haemorrhage we have purposely erred on the conservative side to exclude any possible cases of cerebral thrombosis. We have included only cases with onset while active in persons with hypertension or severe arteriosclerosis and with few exceptions, bloody cerebrospinal fluid. Thus we have found 148 cases of primary intracerebral haemorrhage in the eleven-year period 1928-1938. There were 131 fatalities a mortality rate of 88%. Postmortem examination was performed in sixty-seven cases. The sex incidence was practically equal in both subarachnoid and cerebral haemorrhage. The average age incidence of the cases of spontaneous subarachnoid haemorrhage was forty-six years with 60% of cases under the age of fifty. In primary

TABLE 1  
*Age Incidence and Mortality*

YEARS	SPONTANEOUS SUBARACHNOID HAEMORRHAGE 118 CASES		PRIMARY INTRACEREBRAL HAEMORRHAGE 1-5 CASES	
	Survived	Fatal	Survived	Fatal
10-19	4	0	1	2
20-29	9	6	0	0
30-39	12	9	3	7
40-49	13	17	4	30
50-59	14	11	3	35
60-69	4	15	3	37
70-79	1	1	2	18
80-89	0	2	1	2
	57	61	17	131

intracerebral haemorrhage the average age was fifty-nine years and only 30% of the cases were under the age of fifty.

The autopsy statistics as to the incidence of spontaneous subarachnoid and primary cerebral haemorrhage are obviously more accurate. Seen at autopsy in the same eleven-year period there have been thirty-three cases of massive non-traumatic subarachnoid haemorrhage and sixty-seven cases of primary cerebral haemorrhage. It is of interest that there were nineteen cases of ruptured aneurysm with large intracerebral haemorrhage (as well as subarachnoid haemorrhage). Thus 22% of massive intracerebral haemorrhages encountered in routine autopsies were due to ruptured aneurysm of the Circle of Willis.

CASE HISTORIES TO ILLUSTRATE THE VARIOUS SYNDROMES  
ENCOUNTERED IN PATIENTS WITH  
INTRACRANIAL ANEURYSMS

The following cases are being reported briefly to illustrate the various clinical types associated with intracranial aneurysms. Only rarely do the aneurysms attain a large size and involve neighbouring structures in the absence of frank rupture. The great majority of aneurysms remain very small and give rise to no symptoms prior to the onset of haemorrhage. When a berry aneurysm ruptures, certain well-known symptoms appear which are common to all cases of spontaneous subarachnoid haemorrhage. Other important manifestations may be superimposed, however, depending on the site of the aneurysm in relation to cerebral structures and on the severity of the haemorrhage. Included in these is intracerebral haemorrhage which is a common sequel of ruptured aneurysm. The group of cases with intracerebral haemorrhage will receive particular emphasis because of their importance in diagnosis and prognosis.

*Uncomplicated Spontaneous Subarachnoid Haemorrhage*

By this is implied the condition where the bleeding from a ruptured aneurysm is entirely into the subarachnoid space, as judged by the clinical condition of the patient. There are no signs of involvement of the brain or cranial nerves other than transient effects due to the presence of blood in the subarachnoid space including signs of meningeal irritation, mental retardation, and possibly some impairment of reflex activity, low-grade fever, and elevation of white blood count. All the symptoms subside within a few weeks after the bleeding has stopped.

*Case 1* S V, a labourer, aged 54, had previously enjoyed good health. In September, 1931, while working, he suddenly experienced severe pain in the back of the neck and frontal headache accompanied by vomiting and mental confusion. He was taken home and remained in bed for one week but, failing to improve, he was then brought into hospital. Examination on admission showed him to be a well-developed man complaining of severe, generalized headache and photophobia. He was restless and drowsy, resenting examination and answering questions in monosyllables. He was well oriented for time and place and there was no gross memory defect. The neck was stiff and Kernig's sign was positive. The tendon

reflexes in the legs were difficult to elicit but otherwise neurological examination was negative. General physical examination revealed nothing abnormal except a slight elevation of temperature. The cerebrospinal fluid was under pressure of 160 mm and was a golden yellow colour. Treatment with complete rest in bed and daily spinal drainage resulted in progressive improvement. The patient was discharged from hospital one month after admission free of symptoms and showing no physical signs. He was re-examined in January 1939 more than seven years later. He had been symptom-free since two months after discharge, at which time he had resumed his heavy labouring work and had not missed a day subsequently due to ill health.

This case is typical of a moderately severe spontaneous subarachnoid haemorrhage progressing to complete recovery with no residual symptoms. As so frequently happens the patient has remained free from any symptoms for more than seven years with no recurrence of symptoms despite continuing with his strenuous occupation since three months after the onset.

*Symptoms of Subarachnoid Haemorrhage with Partial or Complete Paralysis of One or More Cranial Nerves*

In these cases the situation of the aneurysm and the severity of the haemorrhage are the determining factors in causing the cranial nerve paralysis and frequently there is residual paralysis of the affected nerve or nerves after recovery from the other symptoms due to haemorrhage.

*Case 2* G. B. a housewife, aged 50 was well until thirty-six hours after receiving a chiropractic adjustment of her neck for a seborrhoeic rash in December 1930. She was awakened at night with severe headache and vomiting the pain mostly referred to the back of her neck. A few minutes later she discovered that the left eye remained closed and she was unable to elevate the lid. The symptoms persisted until her admission to hospital three weeks after the onset. Examination showed a well-nourished young woman moving restlessly in bed and very confused mentally. She was disoriented for time and her memory, perception and attention were all impaired. The neck was very stiff and Kernig's sign was positive. There was ptosis of the left upper eyelid and the left eye was deviated to the extreme left with complete paralysis of the intrinsic and extrinsic muscles supplied by the third nerve. A low-grade fever was present up to 101 degrees the white blood count was 16 000. The cerebrospinal fluid contained gross blood and on centrifuging was deeply xanthochromic.

The patient was treated with complete rest in bed and frequent removal of 10 to 20 c.c. of the bloody fluid. During her three months' stay in hospital she had four recurrences of the bleeding as indicated by increasing severity of her symptoms and fresh blood in the cerebrospinal fluid. Finally her improvement seemed to be sustained and she was allowed to return home where a further period of rest was advised. On discharge the only finding was the complete left third nerve paralysis but the patient complained of headaches and inability to think clearly. Re-examined in January 1939, she stated that during the year following discharge from hospital the headaches gradually lessened in frequency and severity and the feeling of mental dullness improved. During the past seven years she has performed her arduous household duties and has felt perfectly well, apart from the condition of her left eye. Examination showed the ptosis to have recovered but a moderate divergent squint remained and the pupil was large and fixed. The patient has learned to suppress the false image and is not troubled by diplopia.

In this case the aneurysm was presumably situated in the region of the bifurcation of the left internal carotid artery. The onset of the third nerve paralysis simultaneously with the subarachnoid haemorrhage indicates that the damage to the nerve was due to the haemorrhage rather than to pressure by the aneurysm. Apart from the residual third nerve palsy the patient has been free of symptoms for a long period as in Case 1. It is noteworthy that despite several recurrences of bleeding during her period in hospital there has been no recurrence since discharge indicating adequate healing at the site of rupture possibly by walling off or actual thrombosis of the aneurysmal sac.

Although the oculo-motor nerves are more commonly involved in spontaneous subarachnoid haemorrhage due to ruptured aneurysm than are other cranial nerves the second fifth seventh and eighth may be affected in certain cases depending on the situation of the aneurysm. The following patient had involvement of the eighth nerve and the symptoms of cerebellar dysfunction during the acute phase of the illness.

*Case 3* M.F. a domestic aged 39, had been subject to bouts of right-sided headache and buzzing in the right ear occurring about every two months since a minor head injury in 1932. In April 1934 her gait became a little unsteady. In June 1934 she was suddenly seized with a severe

generalized headache, stiffness of the neck and a loud buzzing in the right ear. On admission to hospital, nine days later, she was found to have a stiff neck and was drowsy but mentally clear. There was horizontal nystagmus on deviation of the eyes to the right and to the left and hearing was impaired in the right ear. A moderate degree of incoordination on voluntary movement was noted in the right hand. The reflexes in the arms were sluggish and those in the legs were not elicited. The plantar reflexes were flexor. Coordination tests of the legs with the patient in bed revealed no definite ataxia. The cerebrospinal fluid contained gross blood and on centrifuging was xanthochromic. Under treatment with complete rest in bed and removal of bloody cerebrospinal fluid on several occasions, the patient showed progressive improvement and on discharge six weeks after admission she was symptom-free. Re-examined in November, 1938, it was learned that she had continued with her work as a domestic since discharge from hospital. Apart from occasional right-sided headaches when she stoops or exerts herself unduly and recurrence of the tinnitus in the right ear for one week two months previously she has been entirely free of symptoms. The only finding on examination, was a moderate deafness in the right ear which was shown to be of nerve type.

The localizing signs in this case suggest that the aneurysm was situated in the right cerebellopontine angle possibly arising from the vertebral artery. The signs of cerebellar dysfunction which were manifest during the acute phase of the illness completely subsided with recovery only some mild eighth nerve damage remaining permanently. Rapid improvement in the signs and symptoms of cerebral involvement is common but often difficult to predict when the patient is first seen. Prognosis should accordingly be guarded in the early stages.

#### *Spontaneous Subarachnoid Haemorrhage with Intracerebral Haemorrhage*

In this group are included those cases with definite evidence of extravasation of the blood into the cerebral substance. The usual site is the cerebral hemispheres particularly the frontal and temporal lobes. The fatal cases presented below are of outstanding importance in demonstrating the pathological basis for what we believe is a common clinical syndrome.

*Case 4* A. H., clerk aged 33 was admitted to the Toronto General Hospital in April 1934 because of a right hemiplegia and aphasia. The

history was obtained that in January, 1933, while walking along the street in another city, he suddenly fell unconscious and was taken to hospital. Eight hours later he regained consciousness but had severe headache and considerable vomiting. These symptoms gradually improved so that he was discharged in twelve days. The morning following discharge he was found to have paralysis of the right arm and leg and difficulty with his speech. Apart from a little improvement in speech and the power in his



FIG 14 ENCEPHALOGRAM, APRIL 1934 (CASE 4) FOURTEEN MONTHS AFTER INITIAL HAEMORRHAGE

There is slight diffuse enlargement of the left lateral ventricle with a more marked local enlargement of its anterior horn

right leg, the condition was unchanged until he came under our observation fifteen months later

Examination showed a moderately severe motor aphasia with also gross defect in the comprehension of written and spoken speech. There was severe spastic paralysis of the right upper limb and slight weakness of the right face and leg. No sensory impairment was detected and the visual fields were full. An encephalogram was done which showed a moderate diffuse enlargement of the left lateral ventricle with no shift in the ventricular system (Fig 14)

In view of the patient's age and the history of onset, a diagnosis was made of aneurysm on the left middle cerebral artery with rupture into the frontal lobe. This diagnosis was substantiated by information later obtained from the hospital to which he was first admitted, that the patient had a very stiff neck on admission and that his cerebrospinal fluid was under increased pressure and contained gross blood. The patient was discharged from hospital to lead a restricted life at home.



FIG 15 CASE 4—ENCEPHALOGRAM, NOVEMBER, 1936

The enlargement of the left lateral ventricle has become much greater (see Fig. 14). A faint ring shadow, due to calcification in the aneurysm, is seen just above the left anterior clinoid process.

About one year after discharge he commenced to have generalized epileptiform seizures. These gradually increased in frequency so that he was re-admitted to hospital in November, 1936. Examination at this time showed the motor aphasia to be still severe but his comprehension of speech was better. The right hemiplegia was unchanged from the previous examination. Encephalogram was repeated which showed the left ventricle to be much larger than it had been two and a half years before (Fig. 15). Although the enlargement was diffuse, the anterior horn was proportionately larger than the rest of the ventricle.



The epileptic seizures were well controlled by the administration of uminal. The patient was readmitted for examination again in May, 1938. The aphasia was found to be less severe and the facial weakness had entirely disappeared. The severe spastic paralysis of the arm had changed very little since the onset but the weakness in the leg now caused little disability and the patient was in the habit of walking miles each day. Encephalogram, repeated on this admission, showed still greater dilatation of the



FIG 16 CASE 4—ENCEPHALOGRAM, MAY, 1938

The dilatation of the left lateral ventricle is much greater (see Fig 14 and 15). The local enlargement of its anterior part is very apparent in this photograph.

left lateral ventricle, particularly the anterior horn, than had been present in 1936 (Fig 16). Further substantiation of the diagnosis in this case was obtained in certain of the skull X-rays. A small opaque rounded ring shadow can be seen on the left side lateral to the sella, in the region of the middle cerebral artery. The appearance strongly suggests calcification in the wall of a small aneurysm.

The only clinical evidence of progression since the onset in this case has been the late development of epileptiform seizures. The severe

spastic paralysis of the right arm has remained unchanged and there has been little change in the aphasia but the weakness of the right face and leg have shown a marked improvement. The series of encephalograms obtained over a four-year period showed a progressive ballooning out of the left lateral ventricle particularly in the anterior portion which was adjacent to the haemorrhage. It is of interest that the whole ventricle enlarged indicating a widespread atrophy throughout the hemisphere. The absence of gross distortion of the ventricle and shift of the ventricular system suggests that progressive gliosis is not the principal factor. It is more probable that the relatively large haemorrhage into the corona radiata has caused remote changes in the white matter predisposing to widespread degeneration.

*Case 5* F C an army pensioner aged 47 felt well until August 24 1938 when he was awakened in the morning by very severe occipital headache. This headache persisted and was accompanied by some vomiting. On August 27 he felt better got up from bed and went for a walk. The next morning August 28 his wife heard him fall on the floor and when she saw him he was lying motionless and deeply unconscious with saliva drooling from his mouth. He regained consciousness after four hours but was apparently unable to speak or utter a sound. He was brought to hospital in that state. His past health had been fairly good. Twenty years ago he had a ruptured appendix treated surgically. Four years ago he saw a physician because of shortness of breath and pain in the praecordium and he was told at that time that he suffered from high blood pressure. The history was obtained entirely from his wife.

Examination in hospital on August 28 showed the patient to be conscious but profoundly aphasic. Motor aphasia was almost complete he was unable to say any recognizable word and he uttered only occasional groaning sounds. There were also severe receptive defects so that he understood only very simple questions and was unable to read. He was mildly stuporous but normally oriented and he frequently indicated that he was suffering pain in the left frontal region. Ophthalmoscopic examination showed bilateral papilloedema of 2-3 dioptres. The visual fields could not be satisfactorily tested because of his speech difficulty but there was an unwillingness to look to the right and a suggestion of an hemianopic defect to that side. There was a slight right lower facial weakness otherwise the cranial nerves were normal. The motor functions were normal in neck trunk arms and legs. There was no stiffness of the neck. The tendon

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The dilatation of the left lateral ventricle is much greater (see Fig 14 and 15). The local enlargement of its anterior part is very apparent in this photograph.

left lateral ventricle, particularly the anterior horn, than had been present in 1936 (Fig 16). Further substantiation of the diagnosis in this case was obtained in certain of the skull X-rays. A small opaque rounded ring shadow can be seen on the left side, lateral to the sella, in the region of the middle cerebral artery. The appearance strongly suggests calcification in the wall of a small aneurysm.

The only clinical evidence of progression since the onset in this case has been the late development of epileptiform seizures. The severe

spastic paralysis of the right arm has remained unchanged and there has been little change in the aphasia but the weakness of the right face and leg have shown a marked improvement. The series of encephalograms obtained over a four-year period showed a progressive ballooning out of the left lateral ventricle particularly in the anterior portion which was adjacent to the haemorrhage. It is of interest that the whole ventricle enlarged indicating a widespread atrophy throughout the hemisphere. The absence of gross distortion of the ventricle and shut of the ventricular system suggests that progressive gliosis is not the principal factor. It is more probable that the relatively large haemorrhage into the corona radiata has caused remote changes in the white matter predisposing to widespread degeneration.

*Case 5* F C an army pensioner aged 47 felt well until August 24 1938 when he was awakened in the morning by very severe occipital headache. This headache persisted and was accompanied by some vomiting. On August 27 he felt better got up from bed and went for a walk. The next morning August 28 his wife heard him fall on the floor and when she saw him he was lying motionless and deeply unconscious with saliva drooling from his mouth. He regained consciousness after four hours but was apparently unable to speak or utter a sound. He was brought to hospital in that state. His past health had been fairly good. Twenty years ago he had a ruptured appendix treated surgically. Four years ago he saw a physician because of shortness of breath and pain in the praecordium and he was told at that time that he suffered from high blood pressure. The history was obtained entirely from his wife.

Examination in hospital on August 28 showed the patient to be conscious but profoundly aphasic. Motor aphasia was almost complete he was unable to say any recognizable word and he uttered only occasional groaning sounds. There were also severe receptive defects so that he understood only very simple questions and was unable to read. He was mildly stuporous but normally oriented and he frequently indicated that he was suffering pain in the left frontal region. Ophthalmoscopic examination showed bilateral papilloedema of 2-3 dioptres. The visual fields could not be satisfactorily tested because of his speech difficulty but there was an unwillingness to look to the right and a suggestion of an hemianopic defect to that side. There was a slight right lower facial weakness otherwise the cranial nerves were normal. The motor functions were normal in neck trunk arms and legs. There was no stiffness of the neck. The tendon

reflexes were somewhat exaggerated in the right arm and leg, though there was no weakness. The right abdominal reflexes were sluggish and the right plantar response was extensor. No sensory loss was apparent, though sensory examination was necessarily incomplete. Examination of the heart, chest and abdomen was negative. Blood pressure was 160/95. Lumbar puncture on August 29 showed evenly blood-stained, pink, cerebrospinal fluid, under a pressure of 250 mm of cerebrospinal fluid. The supernatant fluid had a clear, deep yellow colour. Wassermann reaction was negative in cerebrospinal fluid and blood. Urinalysis showed a trace of albumin, a few hyaline and granular casts, and a specific gravity of 1.030. Blood examination showed haemoglobin, 90%, red blood count, 5,000,000, white blood count, 12,000. X-rays of the skull were negative except for slight shifting of the pineal shadow to the right.

The anatomical diagnosis in this case was clearly indicated. The signs were those of a lesion in the left temporoparietal region. The pathological diagnosis seemed more difficult. Though the sudden onset was suggestive of a vascular lesion, the presence of signs of increased intracranial pressure led us at first to consider the possibility of cerebral tumour. However, after the finding of fresh and older blood in the cerebrospinal fluid, the clinical diagnosis was ruptured berry aneurysm in the region of the left carotid bifurcation, with haemorrhage into the left temporal lobe. (In our experience, subarachnoid haemorrhage from a cerebral tumour is extremely rare.) For the first few days in hospital the patient's condition improved generally. He was less stuporous and his headache apparently disappeared, though his neurological signs remained the same. On September 9 he suddenly became worse. He began to breathe stertorously, vomited and rapidly became unconscious. His pupils were widely dilated, the right facial weakness became much greater, and the tendon reflexes were absent in the arms and exaggerated in the legs. There were bilateral extensor plantar responses. Abdominal reflexes were absent. Lumbar puncture now showed clear fluid under the pressure of 435 mm of cerebrospinal fluid. Blood pressure was 230/140. He died three or four hours after losing consciousness.

Autopsy showed a berry aneurysm 1 cm in diameter on the left middle cerebral artery at its first bifurcation (Fig 17 A). There was a recent tear in the upper part of the sac. There was some blood clot in that Sylvian fissure, but the basal subarachnoid cisterns were free of haemorrhage. The aneurysm had ruptured upwards and backwards into the left temporal, parietal and frontal lobe white matter. Sectioning of the brain showed an older, firm, blood clot lying in the upper temporal region, surrounded



FIG. 17 Case 5

A (Left) Shows the aneurysm at the second branching of the left middle cerebral artery in the Sylvian fissure. It has ruptured through its upper surface.  
 B (Right) Horizontal cut surface. In the centre is the round, firm, older hematoma. It is surrounded by the massive fresh fatal hemorrhage.



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remained unconscious two days and then gradually improved. Then however she was found to have a total flaccid left hemiplegia with diminished tendon jerks and an extensor plantar reflex. Neck stiffness and Kernig's sign remained present for about a week. There was also a left hemianopia and a partial right third nerve paralysis indicated by slight ptosis, mydriasis and a slight external squint. With this recurrence of haemorrhage the development of a left hemiplegia and hemianopia suggested intracerebral rupture with involvement of the right internal capsule. The right third nerve lesion was additional evidence of a berry aneurysm in the region of the right carotid bifurcation.

The patient's general condition again improved, the headache and stiff neck subsided and the cerebrospinal fluid cleared, but the left hemiplegia and the right ptosis and mydriasis persisted. On August 26 she began to complain of severe steady pains in the right side of the face throughout the whole trigeminal nerve distribution. On August 28, 1938, she suddenly had a severe and fatal recurrence. There was a sudden occipital headache then deep unconsciousness with death in two hours.

At autopsy a sacular aneurysm measuring 1.3 cm. was found at the junction of the right internal carotid and right posterior communicating arteries (Fig. 18). The right oculomotor nerve was firmly adherent to the aneurysm wall. The aneurysm was partly imbedded in the medial surface of the right temporal lobe and had ruptured into that hemisphere. Sections of the brain showed old firm bloodclot in the basal ganglia and internal capsule and massive fresh haemorrhage lacerating and stripping the white matter with extension into the right lateral ventricle. All of the ventricles were filled with fresh blood. In the anterior basal subarachnoid cisterns there was only a little brownish blood staining. There was considerable fresh blood in the cisterna magna and around the cerebellum which had apparently poured out from the ventricles.

In this case the temporal lobe syndrome of aneurysmal rupture is again well exemplified. First there was a typical subarachnoid haemorrhage, then a second haemorrhage into the temporal lobe via its medial surface with involvement of the internal capsule and a residual hemiplegia. The third massive total haemorrhage again lacerated brain tissue and spread into the ventricles.

Thus we have been fortunate in obtaining pathological verification of temporal lobe and capsular haemorrhage from aneurysmal rupture and the clinical picture is easily correlated. Haemorrhages into one or both frontal lobes from ruptured aneurysms in the region

by massive fresh terminal haemorrhage, forming a large excavation in the left hemisphere (Fig 17 B) The older haemorrhage had apparently occurred on August 28 and its position in the temporoparietal region, below and outside the internal capsule, clearly explained his clinical picture The cerebral arteries showed only slight patchy arteriosclerosis, and no other aneurysms were present

This case is an instructive example of intracerebral haemorrhage into the temporal lobe from rupture of a berry aneurysm Intracerebral haemorrhage in this neighborhood may occur from backward rupture of an aneurysm of the Sylvian fissure, as in this case, or by haemorrhage lateralwards through the hippocampal uncus from an aneurysm at the bifurcation of the internal carotid artery If this patient had survived one would have expected a clinical picture much the same as in case 4

*Case 6* E B, a housewife, mulatto, aged 38, was well until July 18, 1938, when she suffered a sudden severe occipital headache and a few minutes later lost consciousness She was four months' pregnant at that time She had had seven previous pregnancies resulting in five healthy children and two stillbirths In her last pregnancy, for which she was confined at this hospital (May, 1937) she had a mild toxæmia, as shown by headaches, mild oedema of the feet, slight albuminuria, and a blood pressure of 195/120 in the eighth month

When examined in hospital on July 18, a few hours after the onset of her apoplectiform attack, she had regained consciousness, but was very drowsy and complained of severe headache The neck was moderately stiff Neurological examination was negative except for some diminution of the tendon and abdominal reflexes on the left side, and a doubtful left plantar response Pulse—50 Blood pressure—150/90 Temperature—100.2° per rectum Blood Wassermann was negative The cerebrospinal fluid was bright red from even admixture with fresh blood

The clinical picture at first was characteristic of spontaneous subarachnoid haemorrhage, suggesting a ruptured berry aneurysm The patient was kept at complete rest in bed and improved rapidly so that two weeks after the onset she felt quite well and showed no localizing signs The neck rigidity had subsided and the cerebrospinal fluid was clear except for slight xanthochromia

On August 2, 1938, she suddenly cried out and at once became deeply unconscious The cerebrospinal fluid was again grossly bloodstained She

remained unconscious two days and then gradually improved. Then however she was found to have a total flaccid left hemiplegia with diminished tendon jerks and an extensor plantar reflex. Neck stiffness and Kernig's sign remained present for about a week. There was also a left hemianopia and a partial right third nerve paralysis indicated by slight ptosis, mydriasis and a slight external squint. With this recurrence of haemorrhage the development of a left hemiplegia and hemianopia suggested intracerebral rupture with involvement of the right internal capsule. The right third nerve lesion was additional evidence of a berry aneurysm in the region of the right carotid bifurcation.

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Thus we have been fortunate in obtaining pathological verification of temporal lobe and capsular haemorrhage from aneurysmal rupture and the clinical picture is easily correlated. Haemorrhages into one or both frontal lobes from ruptured aneurysms in the region



FIG 18 Case 6

Photograph A (left) shows the meninges at the junction of a right internal carotid and posterior communicating arteries. The third nerve is adherent to the sac. The hippocampus is indicated and the temporal lobe haemorrhagic.

B (right) shows the cut surface with recent and old haemorrhage involving the white matter, internal capsule and basal ganglia.

of the anterior communicating artery and haemorrhage into one frontal lobe from aneurysm in the Sylvian fissure have been observed repeatedly in this series. Unfortunately no verified case had survived long enough to give a clear-cut clinical syndrome. The following fatal case is probably a good example but unfortunately, it was impossible to obtain permission for autopsy.

*Case 7* D. S. aged 56 was well until Christmas Eve 1938. On that occasion while walking downstairs he suddenly lost consciousness and fell a distance of eight steps. He was found there deeply unconscious and put to bed. He remained in that state and was incontinent of urine two or three times though no convulsions were noted. He was brought to hospital on December 25 about twelve hours after the onset. On examination then he was semicomatose and breathing stertorously; he was unable to obey any commands and moved only slightly on painful stimulation. The right arm and leg moved about restlessly; the left limbs were seldom moved. The neck was slightly stiff. There was a conjugate deviation of the eyes to the right; otherwise the cranial nerves were normal. Tone was normal in the limbs and the tendon reflexes were present and equal but the left plantar response was extensor and the left abdominal reflexes were absent. Examination of the skull was negative; there was no evidence of trauma; no bruit; and X-rays of the skull were normal. The fundi appeared normal except for some hyperaemia of the optic discs. Lumbar puncture on December 26 showed a pressure of 125 mm. of cerebrospinal fluid; deep pink bloodstained fluid with mild xanthochromia of the supernatant fluid. The heart was slightly enlarged. Blood pressure was 180/100.

During the first few days in hospital he, at times, improved slightly, regaining consciousness enough to mumble answers to a few questions and to obey a few simple commands. The cerebrospinal fluid was examined repeatedly and cleared progressively so that by December 31 there was only faint pink bloodstaining and a deep yellow xanthochromia.

On January 1, the patient was conscious and generally improved but it was now evident that he was in a demented vegetative state. He was lying in bed motionless except for some plucking at the bedclothes with his left hand. His eyes were open and would at times move to follow the examiner. He was lying with complete unconcern in a mass of faeces and urine. He would occasionally shut his eyes or open his mouth to request. He would at times make attempts to speak but would emit only a mumble in which one could distinguish occasional words. He named



correctly a flashlight and called a fountain-pen a pencil. Examination of the cranial nerves was negative. There seemed to be no hemianopia to rough tests. There was some flexor rigidity in both arms, greater on the left. He moved the right arm to request but not the left. In the weak left hand there was a well-defined grasp reflex. This hand tended to grope at the bedclothes. A gentle stroke across the palm elicited a firm maintained grasp. There was also an exaggerated stretch reflex of those fingers. The right leg was normal. The left leg was apparently paralyzed and showed mild extensor rigidity. The tendon reflexes were normal except for sluggish left knee and ankle jerks. The left plantar was extensor, the right flexor. He remained in this state until January 12 when he became drowsy, developed a fever and showed signs of bronchopneumonia, from which he died on January 15. Permission for autopsy was refused.

This patient presented clearly a clinical picture of subarachnoid and intracerebral frontal lobe haemorrhage. The mild hemiplegic signs on the left with a grasp reflex pointed to destruction in the right frontal lobe. The profound dementia and the rigidity in the right arm suggested involvement also of the left frontal lobe. The clinical diagnosis was haemorrhage into the subarachnoid space and both frontal lobes from a ruptured berry aneurysm in the region of the anterior communicating artery.

#### *Large Aneurysms Without Rupture*

In these cases the clinical findings are due mainly to the pressure exerted on neighboring structures by the enlarging aneurysmal sac. Signs resulting from actual spontaneous subarachnoid haemorrhage are slight or entirely absent during the clinical course. These cases are much less common than those previously described but are of considerable importance from a diagnostic standpoint.

*Case 8.* A B, an unemployed man, aged 49 gave a history of mental symptoms for ten years and organic neurological symptoms for two years. Since 1926 he had been confined to a mental hospital on three occasions because of paranoid ideas with agitated irresponsible behaviour and was diagnosed Paranoid Dementia Praecox. His behaviour was at times quiet and apparently normal at other times excited confused and indecent. In September 1934 a left deafness and facial weakness were found and he was referred to the Toronto General Hospital as a probable case of

acoustic neuroma At this time he was mentally clear and gave the history that two years ago he began to suffer from left tinnitus with frequent occipital headaches For one year he had noticed increasing deafness in the left ear Numbness over the left side of his face had developed during the last six months and for two months there had been nausea diplopia left facial weakness and unsteadiness on walking

Neurological examination showed slight weakness in the left arm and leg nystagmus on looking to the left and left third fifth sixth seventh and eighth cranial nerve palsies Ventriculography revealed marked dilatation of the lateral ventricles A diagnosis of brain-stem tumour was made At operation October 15 1934 a nodular tumour was found in the left cerebello-pontine angle which after haemorrhage was recognized as an aneurysm and hope of surgical removal was abandoned After operation the patient developed a more complete paralysis of the left sixth nerve and the ninth and tenth nerves became involved on that side He ran a high post-operative fever lapsed into coma and died on November 5 1934

At autopsy a large dumb-bell shaped nodular aneurysm measuring  $5 \times 3 \times 2$  cm was seen on the antero-lateral aspect of the left side of the pons filling the cerebello-pontine angle and firmly compressed against the sphenoid bone (Fig 19) The aneurysm was attached by a narrow neck to the trunk of the right vertebral artery at its junction with the basilar The left vertebral artery was small and thread-like The wall of the aneurysm varied in thickness in most places being thin and semi-transparent There was a small patch of calcification in its wall just beyond the neck of attachment to the vertebral artery The contents were firm crumbly brick-red thrombus The bed of the aneurysm showed extreme excavation and distortion of the pons The fifth nerve could not be seen and the nerves from the left side of the upper medulla were severely compressed There was a subarachnoid suffusion of old brownish blood pigment over the whole base of the brain There was a small atheromatous plaque at the origin of the right posterior cerebral artery another on the basilar otherwise no gross arteriosclerotic changes were observed Section of the brain showed a considerable internal hydrocephalus

Examination of the other organs revealed a bilateral acute bronchopneumonia and marked coronary disease of the heart with two old healed infarcts of the myocardium

Microscopic sections of the wall of the aneurysm showed a thin membrane of connective tissue No elastic tissue or smooth muscle were present Organized thrombus was seen in some parts and there was considerable phagocytosed blood pigment There was no evidence of inflammatory reac-

tion Sections of the right vertebral artery proximal to the aneurysm and of the left vertebral and middle cerebral arteries, showed slight nodular

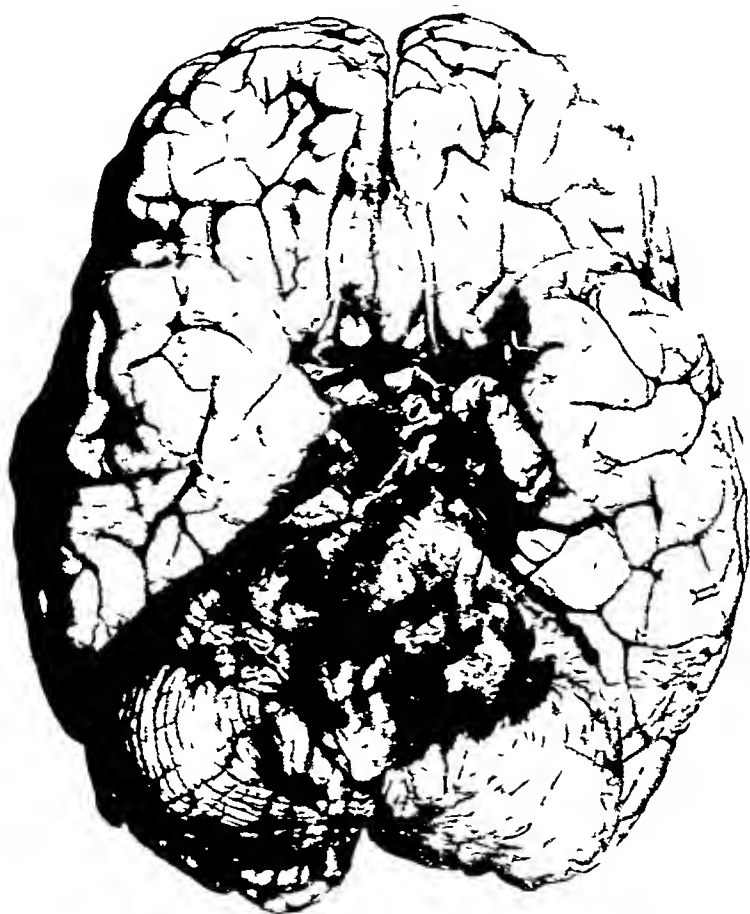


FIG 19 LARGE, UNRUPTURED ANEURYSM (CASE 8) AT JUNCTION OF VERTEBRAL AND BASILAR ARTERIES, COMPRESSING THE MEDULLA PONS AND CEREBELLUM

endarteritis and splitting of the internal elastic lamina but no apparent change in media or adventitia

In this case an unusually large saccular aneurysm arising from the junction of the vertebral and basilar arteries had presented the clinical

picture of mental changes for ten years and finally a typical cerebello-pontine angle syndrome. In retrospect there is no apparent possibility of having made a preoperative diagnosis of aneurysm rather than tumour.

This was much the largest of the intracranial aneurysms recorded in the files of the Department of Pathology, University of Toronto and in fact very few of larger size are reported in the literature. Beadles (1907) reported an aneurysm of the internal carotid measuring  $4.5 \times 2.9$  cms. Wells (1922) case of a vertebral aneurysm which he claimed to be one of the largest, measured  $3.5 \times 3.4 \times 2.0$  cms. Schmidt (1930) mentioned the finding of an intracranial aneurysm the size of a fist, which is the largest on record. In the numerous case reports pathological and clinical counterparts to the above case have been described. Duguid's (1925) case of an aneurysm at the junction of the left vertebral and basilar arteries in a boy of seventeen closely resembled ours in site and in gross morphology. This aneurysm measured  $1.9 \times 1.1$  cms. A fusiform aneurysm of the basilar artery reported by Guillaumin and Schnitzler and Bertrand produced a clinical picture of eighteen months' duration very similar to that of our case. They also made a diagnosis of brain-stem tumour.

It has been stated that aneurysms as well as thrombosis and embolism of the vertebral arteries are more common on the left side than on the right due to the presence of a constriction at the point where the left vertebral artery joins the basilar (Parker 1926, Wells 1922). It is therefore remarkable that the three vertebral aneurysms of our series were all right-sided. In the case here described dissection revealed the origin from the right vertebral though the aneurysm lay over on the left side of the pons.

*Case 9.* F. T. a salesman aged 56 was a pleasant intelligent and successful man until about thirty-five years of age, when his family noticed a marked change in his personality. He became lazy, lost all ambition and was unable to keep a job. He was quarrelsome and thought that everyone was against him. He suffered from periodic attacks of headache with nausea. During the past five years these changes had become more marked. He would become very angry on the slightest provocation then he would become red in the face and sweat profusely. He was slow in performing simple acts and would take an hour to dress. His memory failed markedly.

in the last three years, particularly for recent events. During this period he had twelve attacks in which he lost his speech for a few minutes. He had polyuria and drank a great deal of water. He had a tremendous craving for food, particularly at night. He was not an alcoholic, but small amounts affected him very much.

On examination in hospital in November, 1934, the patient was well-oriented but dull and stuporous, with poor memory. Unfortunately, his mentality prevented examination of the visual fields. Examination of the nervous system was otherwise negative. Blood Wassermann was negative. There were râles at both lung bases and the heart was slightly enlarged. Electrocardiogram showed changes suggestive of coronary thrombosis. On January 24, 1935, he had a severe attack of praecordial pain, following which there was rapidly progressive cardiac failure with death on February 6, 1935. His blood pressure ranged from 210/140 to 140/80.

Postmortem examination revealed severe coronary disease of the heart with extensive fibrosis of the myocardium. There was aneurysmal dilatation of the left ventricle which contained mural thrombi.

Examination of the brain after fixation showed a large aneurysm arising from the angle formed by bifurcation of the basilar artery. The basilar artery appeared elongated, and the aneurysm had developed in a surprising position, projecting forward above the optic chiasm to lie mainly between the two frontal lobes on top of the anterior cerebral and communicating arteries. The relations of the aneurysm were best seen in a sagittal section of the brain (Fig 20). The sac measured 3.5 x 2 cm. and was filled by firm, laminated, old thrombus. The outer surface of the sac was thin, dark reddish and smooth except for a few firm yellowish arteriosclerotic plaques. The posterior surface of the aneurysm bulged slightly into the third ventricle, being separated from this cavity by only a thin lining. There was marked compression atrophy and distortion of the posterior part of the medial surfaces of both frontal lobes, the genu and rostrum of the corpus callosum, and of the mammillary bodies. There was a moderate dilatation of the lateral ventricles. There was old haemorrhage on the frontal lobe cortex and the corpus callosum.

The arteries at the base of the brain showed [severe] nodular [arterio-sclerosis].

Microscopic examination of the aneurysm wall showed it to be entirely fibrous with no muscle or elastic tissue. There was considerable phagocytosed blood pigment mainly in the outer part of the wall. There was some organization of the thrombus at its margin. The compressed frontal lobe tissue showed almost complete loss of nerve cells, heavy gliosis and old haemorrhage.

In this case a large aneurysm lying between and compressing both frontal lobes had resulted in a prolonged and severe organic dementia. It is unfortunate that a more detailed neurological examination was not possible. In retrospect it seems certain that there was optic atrophy probably a bitemporal hemianopia and some degree of anosmia. Pathologically this case is unique in that the aneurysm



FIG 20 LARGE UNRUPTURED ANEURYSM ARISING AT BIFURCATION OF BASILAR ARTERY AND BELIEING FORWARD ABOVE OPTIC CHIASM AND BETWEEN FRONTAL LOBES (CASE 9)

had arisen at the basilar bifurcation and projected forward into the anterior prechiasmal position

#### SURVEY OF CLINICAL OBSERVATIONS IN 126 CASES

##### *Nature of Onset of Spontaneous Subarachnoid Haemorrhage*

*Relation to Exertion* In the great majority of cases the onset was sudden, often without any premonitory symptoms in a person apparently perfectly well. In a small proportion of cases (10% in this series) the symptoms developed gradually over several hours or even days. As indicated in Table 2, the onset occurred during ordinary routine activity in the majority of the patients. It is probable that most of those who were found unconscious at home also belong to this group. The next largest group includes those cases where the onset

occurred during sleep or on awakening. The frequency of the cases with an onset at this time is surprising and contrasts with the history usually obtained in primary intracerebral haemorrhage. Though it has been shown (Gibbs et al 1935) that the blood flow through the brain is not decreased during sleep, the individual is not subject to as great fluctuations of blood pressure as occur during daytime activity. In only fourteen cases was there a history of onset during some unusual exertion such as a boisterous party, an argument, swimming, running upstairs, post-operative vomiting, etc. Mild trauma such as a slap on the back, a sudden jolt while driving, and a

TABLE 2  
*Onset of Spontaneous Subarachnoid Haemorrhage in Relation to Bodily Exertion*

	TOTAL	FATAL
Sudden onset of symptoms		
During ordinary activity	55	31
During sleep or on awakening	16	7
During unusual exertion	14	7
Found unconscious on floor at home	8	7
Immediately following mild trauma	3	0
While in bed with acute infection	1	1
Gradual onset of symptoms		
During ordinary activity	10	5
Following trauma	1	0
Total	108	57

fall, precipitated the sudden onset of severe haemorrhage in three cases respectively and a fall without head injury initiated the symptoms in one case where the onset was gradual.

*Summary* In this series, spontaneous subarachnoid haemorrhage showed an abrupt, sudden onset in 90 per cent of cases. The patient was at rest in bed, standing, or walking in 78 per cent of cases, and undue muscular exertion was known to precipitate the onset in only 18 per cent. It is probable, then, that the rupture of an aneurysm sac is usually a gradual process of stretching and haemorrhagic dissection, and in only a few cases is the tear culminated by a sudden increase in blood pressure due to violent muscular efforts.

*Early Symptoms* Headache was the first symptom in eighty-three cases and almost invariably it was extremely severe. Characteristically the headache was generalized and excruciating, tending to predominate in the occipital region, the pain extending down the back of the neck. In a number of cases, however, the initial headache was distinctly localized in character, namely, unilateral occipital, bilateral frontal, behind one eye, or at the vertex. In most instances vomiting occurred soon after the onset of headache, but in two cases vomiting was the first symptom. The next most common initial symptom was loss of consciousness. This occurred as the first manifestation in twelve cases and seventeen other patients were found unconscious or became unconscious within a few minutes of experiencing the first symptom. Other less common symptoms at the onset included vertigo, irrationality, convulsions, numbness or weakness in hemiplegic distribution, visual symptoms, prostration, chills, speech disturbances, and pain in the back and lower limbs.

In addition to the twenty-nine cases with loss of consciousness as an initial symptom, thirty-one other patients lost consciousness within a few hours of onset. The high incidence of loss of consciousness at the onset or shortly afterward in this series is not in accord with the observations of Merritt, 1938. He states that it is rare for consciousness to be lost at the onset in spontaneous subarachnoid haemorrhage, in contrast to primary intracerebral haemorrhage. Of the sixty patients with loss of consciousness in this series, thirty-seven progressed to a fatal termination, with only ten regaining consciousness before death, for periods varying from several hours to eight days. Most of the recovered cases suffered periods of unconsciousness lasting only a few hours, though there were five cases who survived after having been unconscious for intervals of one to eight days.

In contrast to the frequency of unconsciousness at the onset is the relative infrequency of convulsions—9 per cent in this series. We cannot agree with Merritt, 1938, however, who believes that an onset with convulsions is of diagnostic value in distinguishing between primary intracerebral haemorrhage and spontaneous subarachnoid haemorrhage. In his series of cases with primary intracerebral haemorrhage, only 14 per cent had convulsions at the onset or within a few days subsequently, which is not significantly different from the percentage in our series.



occurred during sleep or on awakening. The frequency of the cases with an onset at this time is surprising and contrasts with the history usually obtained in primary intracerebral haemorrhage. Though it has been shown (Gibbs et al 1935) that the blood flow through the brain is not decreased during sleep the individual is not subject to as great fluctuations of blood pressure as occur during daytime activity. In only fourteen cases was there a history of onset during some unusual exertion such as a boisterous party, an argument, swimming, running upstairs, post-operative vomiting, etc. Mild trauma such as a slap on the back, a sudden jolt while driving, and a

TABLE 2

*Onset of Spontaneous Subarachnoid Haemorrhage in Relation to Bodily Exertion*

	TOTAL	FATAL
Sudden onset of symptoms		
During ordinary activity	55	31
During sleep or on awakening	16	7
During unusual exertion	14	7
Found unconscious on floor at home	8	7
Immediately following mild trauma	3	0
While in bed with acute infection	1	1
Gradual onset of symptoms		
During ordinary activity	10	5
Following trauma	1	0
Total	108	57

fall precipitated the sudden onset of severe haemorrhage in three cases respectively and a fall without head injury initiated the symptoms in one case where the onset was gradual.

*Summary.* In this series spontaneous subarachnoid haemorrhage showed an abrupt sudden onset in 90 per cent of cases. The patient was at rest in bed, standing or walking in 78 per cent of cases and undue muscular exertion was known to precipitate the onset in only 18 per cent. It is probable then that the rupture of an aneurysm sac is usually a gradual process of stretching and haemorrhagic dissection and in only a few cases is the tear culminated by a sudden increase in blood pressure due to violent muscular efforts.

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*Summary* Severe generalized headache radiating down the back of the neck, frequently associated with vomiting, was the first symptom in a majority of the cases. Loss of consciousness was the next most frequent manifestation at the onset. Convulsions as an initial symptom were relatively uncommon.

*Constitutional Disorders, Symptoms and Precipitating Factors Preceding the Onset of Spontaneous Subarachnoid Haemorrhage* In 50 per cent of the cases there was no history of any symptoms whatever

TABLE 3

*Conditions Preceding the Onset of Haemorrhage in 59 Cases of Subarachnoid Haemorrhage*

	TOTAL	FATAL
Hypertension and associated symptoms	16	10
Trauma	10	6
Headaches and vertigo	6	3
Migraine	4	1
Headaches and visual disturbance	4	0
Pregnancy	3	2
Vertigo	2	1
Progressive dementia	2	1
Headaches and ataxia of legs	2	1
Postoperative vomiting	2	2
Headaches and progressive dementia	1	1
Headaches	1	1
Epilepsy and chronic alcoholism	1	0
Diabetes mellitus	1	0
Tabes dorsalis	1	1
Idiopathic epilepsy	1	0
Erysipelas facialis	1	1
Head cold	1	1
Total	59	32

prior to the onset and no underlying disease was found on examination in hospital. Evidence of constitutional disease or a history of previous ill-health or trauma was obtained in fifty-nine cases (Table 3). The various conditions recorded in the table will now be briefly discussed.

*Constitutional Disorders* Hypertension was the only constitutional disorder that occurred with sufficient frequency to be regarded as more than incidental. Each of these sixteen cases had findings or a history

indicating hypertension prior to the onset and the pressure remained elevated in those that recovered from the haemorrhage. The presence of an elevated blood pressure on examination after admission was not of itself regarded as significant. Commonly, during the acute phases of the illness, patients may show an elevation of the systolic and diastolic pressure of a transitory nature which subsides as their general condition improves.

A history of migraine was recorded in four of the cases in this series, only one of which was fatal. This latter case came to autopsy but no definite association between the headaches and the aneurysm could be detected clinically or pathologically. The infrequency of migraine in this series lends no support to the theory postulated by Adie, 1930, that migraine is closely related to intracranial aneurysms, at any rate to those which proceed to rupture. The four cases had all suffered migrainous headaches since early life and in two cases there was a family history of migraine. It is of interest that these two patients have both been free of migrainous headaches since the attacks of spontaneous subarachnoid haemorrhage which occurred four and five years ago respectively. In only one patient was there evidence from the situation of the headache that the two conditions were associated. This patient suffered a right-sided headache, similar in type and situation to her usual migrainous headache, at the onset of haemorrhage. A left hemiplegia developed with the other symptoms of spontaneous subarachnoid haemorrhage, indicating that the aneurysm was situated on the right side of the Circle of Willis. There was no case of so-called ophthalmoplegic migraine in this series. This condition is probably always due to leaking aneurysms, as suggested by Bramwell, 1934, but it is unlikely that any close relationship exists between migraine, not associated with ocular palsies, and intracranial aneurysms.

Only one case of cerebrospinal syphilis was recorded in this series. Syphilis has frequently been considered a possible cause of spontaneous subarachnoid haemorrhage (Smith, 1924; Weidman, 1915; Sands, 1929), but the evidence has not been convincing. It is obviously not justifiable to conclude a syphilitic origin for the haemorrhage simply because a patient happens to have syphilis. Probably a considerable proportion of the cases of spontaneous subarachnoid haemorrhage ascribed at autopsy to syphilitic arteritis with recovery have not been

carefully searched for an aneurysm. Sands described two cases, one fatal, which he attributed to syphilis. He makes no mention of having examined the arteries at the site of bleeding for aneurysm. The large series presented here would seem to demonstrate that syphilis is not an important factor in the causation of spontaneous subarachnoid haemorrhage because examination of blood and cerebrospinal fluid was carried out in practically every case. It is conceivable that an active syphilitic process in the brain may precipitate the rupture of a co-existing berry aneurysm. This might account for those cases reported in which spontaneous subarachnoid haemorrhage has occurred during the course of an active cerebral syphilitic process. It might also explain some of the greater frequency of syphilis, 4 per cent to 9 per cent, in other series of cases (Symonds, 1924, Herman, 1926, Strauss and Tarachow, 1937).

*Preceding Cerebral Symptoms Probably Associated with the Presence of a Berry Aneurysm.* Although the onset is usually abrupt there may be occasionally mild premonitory symptoms preceding the development of severe manifestations by several hours or even days. Preceding cerebral symptoms of longer duration than this are uncommon and occurred in only eighteen cases of this series. They included headaches, vertigo, visual disturbances, ataxic gait and progressive dementia. These symptoms were present for periods of from one month to ten years prior to the onset of severe haemorrhage. Headache was the commonest symptom, occurring in fourteen cases, but in nearly every instance it was accompanied by other manifestations. Vertigo was the next most common symptom, usually occurring in attacks initiated by changes in posture.

Three of the patients with visual disturbance complained of progressive visual failure and another patient had diplopia. The average duration of these symptoms prior to the onset of the haemorrhage was about two months. The proximity of certain common aneurysmal sites to the optic and oculomotor nerves undoubtedly determined the symptoms in these cases, none of which were fatal. The observation that most aneurysms rupture when still very small makes it probable that the nerves were involved by leakage of blood from the aneurysms rather than by direct pressure.

The two remaining premonitory symptoms, severe ataxic gait and

progressive dementia, may be indicative of gross interference with cerebral function. The five cases in which they occurred all presented, clinically or at autopsy, evidence of intracerebral as well as subarachnoid haemorrhage at the time their acute symptoms brought them under observation. The two fatal cases in which the lesion was verified at autopsy had both become progressively demented for more than a year prior to the onset of acute symptoms. The haemorrhage had originated in the region of the anterior cerebral arteries with gross extravasation of blood into one frontal lobe in both cases. In neither was there evidence of vascular disease in the brain to account for the dementia, and the extent of the terminal haemorrhage made it impossible to demonstrate what had taken place previously at the site of aneurysm. It is possible, however, that in these cases, repeated leakage of blood from the aneurysm had occurred intracerebrally before the onset of frank rupture, causing the disturbance in cerebral function.

It is probable that the majority of premonitory symptoms are the result of recurrent small leakage from the aneurysms. The bleeding may be entirely subarachnoid or, less commonly owing to the situation of the aneurysm it may invade cerebral tissue. In the former event the symptoms are likely to be intermittent with headache predominating, whereas, with involvement of cerebral tissue, the symptoms are likely to be local and of a more disabling character.

*Incidental Conditions and Trauma* The presence of such conditions as uncomplicated pregnancy, upper respiratory infections, and erysipelas at the onset, was so infrequent in this series that they can scarcely be regarded as being very significant precipitating factors. The onset occurred within two days after abdominal operations in two cases and was probably determined by postoperative vomiting in both instances.

A definite history of trauma, in most cases to the skull, was obtained in only ten cases. In all instances the trauma occurred within six months of the onset. In four cases the onset of symptoms dated directly from a mild head injury. In two cases a preceding mild trauma had occurred within one week of the onset. The remaining four cases had a longer interval between the injury they sustained and the onset of symptoms due to haemorrhage, but in these four the

trauma was of such severe character that a relationship between the two events seemed possible

*Summary* In the great majority of the cases there was no history of trauma, infection, or any other condition which could be regarded as a predisposing cause for occurrence of the haemorrhage

### *Findings on Examination*

*Physical Signs Due to Subarachnoid Haemorrhage* Marked stiffness of the neck was found in practically all cases, often associated with a positive Kernig's sign. Only occasionally was there actual head retraction but, as a general rule, any movement of the neck was painful. The only mental change in the majority of cases of uncomplicated spontaneous subarachnoid haemorrhage was a mild general retardation of memory, perception, and attention. Occasionally, however, cases were encountered with severe mental disturbances in which there were no other signs of intracerebral extension of the haemorrhage. The symptoms in these cases included profound impairment of memory, apathy, depression, extreme restlessness and irritability. The fact that improvement in the mental status occurred rapidly concomitant with the subsidence of other signs was taken as evidence that the symptoms were due to the effects of the subarachnoid haemorrhage alone and not to intracerebral haemorrhage.

Occasionally the pupillary reactions may be sluggish and the tendon reflexes in the legs markedly reduced in activity during the acute stages of the haemorrhage. Bilateral dorsiflexion on plantar stimulation without loss of power in the legs may also be present. These reflex changes also disappear rapidly with improvement in the patient's general condition and are, therefore, probably the result of subarachnoid haemorrhage affecting the cerebral cortex and spinal nerve roots. Some low-grade fever and a mild elevation of the white blood count are frequently present for the first few days after the onset.

Papilloedema and fundal haemorrhages, together or separately, were found in twenty cases in this series, of which twelve were fatal. The average age of the twenty patients was approximately fifty years and only three were under forty. In considering the incidence of papilloedema, we did not include cases where the finding was at all doubtful, so that we may well have omitted some cases with early

changes. In seven cases there was papilloedema only. In six cases there were haemorrhages without papilloedema and in the remaining seven both papilloedema and haemorrhages were present. In two cases the haemorrhages were subhyaloid the remainder were situated in the retina. The incidence of papilloedema and haemorrhages was greater in the fatal cases suggesting that their presence is some index of the severity of the spontaneous subarachnoid haemorrhage. In all but one case with these findings the cerebrospinal fluid pressure was elevated in hospital and in fourteen cases the pressure was over 300 mm.

Griffith Jeffers and Fry 1938 have commented on the infrequency of papilloedema despite the high cerebrospinal fluid pressure so commonly present in spontaneous subarachnoid haemorrhage. From the results of experimental work they infer that blood in the cerebrospinal fluid in sufficient amounts will block the perineural spaces preventing papilloedema. In a minority of cases the block is incomplete and papilloedema occurs if other predisposing factors are present such as (1) partial ventricular block so that there is relatively little blood in the subarachnoid space (2) malignant hypertension, (3) glioma, and (4) sinus thrombosis.

It will be noted that six (43 per cent) of the patients with papilloedema in this series had no hypertension in hospital and no history of hypertension. There were no reasons in these cases to suspect the presence of any of the other predisposing factors enumerated above. One would consider that the rapidity of onset of severe haemorrhage and the situation of the source of the bleeding might be important factors in determining the presence of papilloedema and haemorrhages. Analysis of our cases tends to support this view. Eight of the fourteen cases with papilloedema were admitted within twenty-four hours of the onset, at which time the findings were present. The remaining cases were admitted from one to nine days after the onset so that it was impossible to say when the findings developed but it is noteworthy that in all fourteen cases the symptoms and signs justified the conclusion that the haemorrhage was of a severe character. Five of the fatal cases came to autopsy and three of these showed the site of rupture to be in the anterior cerebral region. The remaining two had aneurysms on the internal carotid and middle cerebral respectively.



One other fatal case had amblyopia as the first symptom, suggesting that the rupture occurred from an aneurysm situated on the anterior part of the Circle of Willis

It is probable that the disturbance in venous return which occurs in spontaneous subarachnoid haemorrhage and manifests itself as papilloedema or haemorrhages in the fundus is to a large extent determined by the initial severity of the haemorrhage and the proximity of the site of rupture to the subarachnoid sheath of the optic nerve

*Cerebrospinal Fluid* In this work we have made no detailed study of the cerebrospinal fluid in regard to the progressive haemolytic changes and cellular reaction It is well known that the spinal fluid is evenly bloodstained soon after the onset of bleeding, and that the bloody fluid does not clot on standing In succeeding days, the blood gradually disappears and the haemolysis results in a changing colouring of the fluid, at first the supernatant fluid is clear, then pale yellow, then deep chrome yellow, then gradually paler and finally clear In the later stages a number of white blood cells are present in the spinal fluid, chiefly mononuclears A detailed study of this pigmentation and cellular reaction was made by Froin, and published in 1904 in his monograph "*Les Hemorrhagies sous Arachnoidiennes*"

In the cases of subarachnoid haemorrhage here reported, twenty-four have been selected in which numerous cerebrospinal fluid examinations were made A review of these examinations was carried out to determine (1) the time until fresh blood disappears from the fluid, (2) the time until xanthochromia appears, and (3) the time required for the fluid to return to its normal, clear, colourless state In some of these cases the figures were only approximate in that punctures were not done every day, and because one cannot always ascertain the exact time of the onset of the haemorrhage

Fresh blood, shown by the presence of red blood cells, disappeared in periods varying from four to nineteen days (8, 12, 9, 6, 19, 10, 15, 10, 7, 7, 7, 14, 8, 6, 4, 9, 8, 9, 12, 6, 6), an average of nine days

Xanthochromia was found within twenty-four hours in six cases, and probably in twelve hours in three of those Xanthochromia was first detected twenty-four to forty-eight hours after the onset of symptoms in three cases, in forty-eight to seventy-two hours in two cases, and in seventy-two to ninety-six hours in three cases In many

other cases xanthochromic supernatant fluid was first seen in the second lumbar puncture from four to eight days after the onset but in these the haemolysis had probably developed at an early stage though not looked for. All that can be stated from the limited findings is that xanthochromia may develop in twelve hours, is usually present twenty-four hours after the onset of headache, but may not be seen until the third or fourth day.

The fluid returned to its normal, clear, colourless state in periods varying from ten to thirty-nine days (30, 13, 24, 21, 24, 12, 15, 20, 16, 10, 19, 25, 24, 39), an average of twenty days.

In several cases an increase of mononuclears was noted in the cerebrospinal fluid in from two to four weeks after the onset, with counts ranging from sixteen to 320 cells. Total protein estimations were done in only a few cases and these were on bloody fluid, showing values from 28 to 100 mgm per c c. The Pandy test, which was performed in the majority of cases, was always positive, varying from 1+ to 4+. Colloidal gold and mastic curves done on the bloody fluid frequently showed slight alterations, such as 1111222110, and 2111121000.

*Localizing Signs.* The incidence of involvement of cranial nerves and cerebral tissue by the haemorrhage is indicated in Table 4. It will be noted that hemiplegia, which occurred in thirty-four cases, was by far the commonest manifestation. There were twelve cases with monoplegia, quadriplegia or hemi-anaesthesia and ten cases with aphasia and hemianopia together or separately, without hemiplegia. Much less common manifestations of cerebral involvement detected in this series were gross persistent dementia in the absence of any other signs and one instance of a cerebellar syndrome. Six cases showed no definite localizing signs on examination in hospital but at autopsy massive intracerebral haemorrhage was found in all instances. Five of these patients were deeply unconscious on admission and the only definite findings were fixed pupils, bilateral dorsiflexion and convulsions. No localizing signs were detected in the other patient who was conscious on admission but the following day he died suddenly in bed. Evidence of cranial nerve paralysis was found in eighteen cases but in nine of these other cerebral structures were affected as well. The oculo-motor nerves were the most commonly involved with the fifth and seventh nerves next in order of frequency. No instances

of paralysis of the ninth, tenth, eleventh or twelfth nerves were noted in this series

Thus, sixty-two patients in this series (53 per cent) had evidence of destruction of cerebral tissue other than cranial nerves. In almost all cases the signs indicated involvement of the cerebral hemispheres and in nineteen instances such lesions were verified at autopsy. Thus the clinical findings are in keeping with the previously described postmortem examination, and altogether it seems quite clear and im-

TABLE 4  
*Summary of Neighbourhood Signs—71 Cases*

	TOTAL	FATAL
Hemiplegia (aphasia in 12 cases)	34	20
(With hemianaesthesia)	7	4
Cranial nerves—2, 3, 4, 5, 6, 7, 8	18	8
(With other gross involvement)	9	6
(Without other gross involvement)	9	2
Aphasia without hemiplegia	6	3
Homonymous hemianopia with hemiplegia	5	3
Homonymous hemianopia without hemiplegia	4	1
Quadriplegia	5	5
Monoplegia	6	4
Hemianaesthesia without paresis	1	0
Cerebellar syndrome	1	0
Severe mental impairment	2	0
Convulsions	9	5
Jacksonian	3	2
Generalized	6	3

Six cases with no localizing signs on examination showed massive rupture into brain at autopsy

portant that aneurysms of the Circle of Willis frequently cause extensive intracerebral haemorrhage as well as subarachnoid haemorrhage. Cases 4, 5, 6, and 7 have been reported at length above to illustrate such aneurysmal haemorrhage. In the literature on spontaneous subarachnoid haemorrhage one repeatedly encounters statements such as the following: "Significant negative findings are the absence of a hemiplegia, other focal signs or choked discs", "With rare exception focal signs indicate that the haemorrhage is intracerebral" (meaning primary intracerebral haemorrhage) (Merritt, 1938),

"There is no gross cerebral localization in these cases" (Ayer, 1934) However, some reference has been made to this aspect of aneurysmal rupture by Courville and Olsen 1938

*Clinical Localization of Intracerebral Haemorrhage from Ruptured Berry Aneurysms* Attempts to correlate the clinical manifestations with autopsy findings indicate that localization of the site of the haemorrhage is usually possible although occasionally cases show massive intracerebral haemorrhage at autopsy which had not been recognized clinically. As we have already pointed out the frontal and temporal lobes are much more commonly involved by the haemorrhage than other portions of the brain. The parietal lobe was frequently invaded secondarily but it was rarely the primary site of intracerebral extension of the haemorrhage. The clinical manifestations vary depending on the situation and extent of the haemorrhage in the respective areas but a brief description of certain syndromes which have been pathologically verified will be attempted.

Invasion of the frontal lobes by haemorrhage usually results from ruptured aneurysms situated on the anterior cerebral, anterior communicating and middle cerebral arteries. When this occurs the symptomatology depends on the site and extent of the frontal lobe involvement. Contralateral hemiparesis was the commonest manifestation varying, according to the severity of the haemorrhage, from a slight weakness with alteration in reflexes to a severe hemiplegia with motor aphasia. Frequently the paresis was confined to or maximum in one leg rarely in both legs. Intellectual retardation was the other principal finding in cases with frontal lobe damage. It differs from that commonly present during the acute phases of spontaneous subarachnoid haemorrhage in that it is more severe and tends to persist. If, as not infrequently happens with ruptured aneurysms situated on the anterior cerebral and anterior communicating arteries the haemorrhage invades both frontal lobes from the medial surface, very severe and permanent dementia is likely to result. Cranial nerve involvement is not commonly associated with frontal lobe invasion but symptoms referable to the second nerve may sometimes be encountered such as a transitory amaurosis or amblyopia.

Haemorrhage into the temporal lobe usually results from ruptured aneurysms situated on the carotid bifurcation or in the Sylvian fissure

The most consistent manifestation of temporal lobe invasion is a homonymous visual field defect. If the lesion is left-sided a severe aphasia is likely to be present also. Involvement of certain cranial nerves, particularly the oculomotor and fifth nerves on the side of the lesion, is commonly associated depending on the site of the aneurysm. As in the case with frontal lobe haemorrhage, bleeding into the temporal lobe may spread medially to involve the pyramidal fibres giving rise to a hemiplegia. In the former, however, the paresis is frequently maximum in the leg whereas in the latter it is often maximum in or confined to the face (see Case 5). Extension from the temporal lobe is likely to involve the sensory as well as the motor tracts and anaesthesia often accompanies the paralysis.

In some instances bleeding extends directly into the ventricles by penetration of the genu of the corpus callosum. When this occurs there may be profound coma, dilated fixed pupils and bilateral dorsiflexion. These findings do not necessarily indicate intraventricular extension of the haemorrhage, however, because they were present in two of our cases where, in each instance, bleeding was confined to the temporal lobe. The signs in these cases were presumed to be due to pressure of the crus against the tentorium.

It has already been mentioned that paralysis of certain cranial nerves may be the only localizing sign or may be associated with other evidences of cerebral damage. The occurrence of cranial nerve paralysis is dependent on the proximity of the nerve or nerves to the site of the bleeding. The third and sixth nerves were by far the most frequently affected, one or both being paralyzed in eight cases. The frequency with which these nerves are involved is probably due to their close anatomical relationship to the internal carotid and the commencement of the middle cerebral arteries which are common sites for intracranial aneurysms. The fifth nerve was affected in five cases. Pain in the distribution of one or more of its branches, most commonly the ophthalmic, was almost as frequent a manifestation as motor or sensory paralysis.

Other cranial nerves found to be affected by the haemorrhage in this series were the second, seventh and eighth. It cannot be definitely stated that the first nerve escaped in all cases because it was not tested with sufficient accuracy but the ninth, tenth, eleventh and twelfth were not involved. Facial paresis of a character indicative

of peripheral seventh nerve involvement was infrequent, occurring in only two cases. The eighth nerve was affected in one case (see Case 3).

We do not feel satisfied that all cases with involvement of the optic nerves or tracts in this series were recognized. Owing to the difficulty of testing acutely ill patients for field defects and visual acuity, it is probable that mild degrees of impairment may have been overlooked. It is unlikely, however, that well-marked and persistent findings were missed. In only two of our cases were definite findings obtained indicating involvement of the optic nerves or chiasma. One patient had a history of gradual visual failure for three months before the onset of haemorrhage and optic atrophy was found on examination. The other patient had no complaints of visual disturbance but a bitemporal hemianopia was detected which gradually subsided while he was under observation. The histories in a number of cases indicated complaints of defective vision before or at the onset of the haemorrhage but, apart from the two recorded above, examination in hospital revealed no definite abnormalities. Jefferson, 1937, found a much higher incidence of involvement of the optic nerves, chiasma and tracts in his series. However, he attributes homonymous hemianopia, in patients with spontaneous subarachnoid haemorrhage from a ruptured aneurysm, to involvement of the optic tracts by the haemorrhage. He suggests that if the hemianopia persists it is probably the result of thrombosis of the posterior cerebral artery, predisposed to by aneurysm. This author makes no reference to direct involvement of the optic radiation by haemorrhage as a cause for the hemianopia although he quotes Symonds as having twice observed compression of the optic radiation by false sacs originating in posterior cerebral aneurysms. In our series nine patients were found to have homonymous field defects. From a consideration of each individual case and the associated symptoms and signs, it is our belief that the hemianopia was the result of extension of the haemorrhage to involve the optic radiation in all instances. Verification of this lesion was obtained at autopsy in three of the cases.

#### *Symptoms of Large Unruptured Aneurysms*

Eight cases of large unruptured aneurysms have been studied, of which five were males and three females. The average age was forty-six. The presence of the aneurysm was verified in six cases, four by

autopsy, one by angiography and one by operation. Only one case had no symptoms, the aneurysm having been found accidentally at autopsy. The other seven cases all had symptoms due to involvement of neighboring structures by the aneurysm. In five cases the aneurysm was situated on the internal carotid artery and the usual onset of symptoms in this situation tended to be rapid with headache and pain behind the eye preceding the development of third nerve paralysis. Of the remaining three cases, the aneurysm was situated on the basilar artery in two and on a vertebral artery in one. In these situations the aneurysm has more room to expand and symptoms usually develop much more gradually than is the case with aneurysms on the internal carotid artery. The patient with an aneurysm on the vertebral artery developed a gradually progressive psychosis with cranial nerve paralysis over a period of ten years. In only one of the cases of basilar artery aneurysm did a pontine syndrome develop. This occurred fairly suddenly following three years of increasing headache. The other case had shown progressive dementia accompanied by headache and petit mal seizures for a period of twenty-one years, the aneurysm having expanded forwards to compress the medial surface of both frontal lobes.

The important feature of these large aneurysms is the resemblance they may bear to cerebral neoplasm in their clinical course. Symptoms are produced by pressure of the gradually expanding mass and differentiation may only be possible by angiography or at operation. The former method is of great value if the possibility of aneurysm is considered in the differential diagnosis of expanding lesions at the base of the brain.

### *Diagnosis*

In the majority of cases the diagnosis of aneurysmal haemorrhage is not difficult. The sudden onset, in a person previously well, of severe headache and prostration, with the findings on examination limited to signs of meningeal irritation and possibly diminished reflexes in the lower limbs, presents a characteristic clinical picture. When, in such a case, the cerebrospinal fluid contains blood and the supernatant fluid is xanthochromic after centrifuging, no doubt can exist regarding the diagnosis. The nature of the onset and the cerebrospinal fluid

findings readily distinguish it from meningitis. Haemorrhagic encephalitis should seldom give difficulty in diagnosis because of its extreme rarity and the difference in the onset and clinical course.

The sudden onset of cranial nerve paralyses, usually oculomotor, in a person previously well should always suggest the possibility of intracranial aneurysm. If the patient is seen early the accompanying signs of subarachnoid haemorrhage are likely to be present, confirming the diagnosis of ruptured aneurysm. If these signs have been relatively slight and the patient is not examined until some weeks after the onset, the diagnosis becomes more difficult. Certain other conditions, such as encephalitis, disseminated sclerosis, syphilis, and cerebral neoplasm may then have to be considered but the nature of the onset and severity of the pain usually enables the diagnosis to be made. Angiography with thorotrast has proven particularly helpful in revealing the aneurysm in cases of this type.

When haemorrhage from a ruptured aneurysm invades the brain substance it becomes necessary to differentiate the case from one of primary intracerebral haemorrhage. The history and findings on examination render the diagnosis possible in most cases but occasionally there is great difficulty in distinguishing the two conditions. Patients with a preceding vascular hypertension present the greatest problem in this regard. In such a case with deep unconsciousness, a hemiplegia and bloody cerebrospinal fluid, it may be impossible to arrive at the correct diagnosis. In primary intracerebral haemorrhage there may be mild premonitory symptoms but paralysis nearly always appears at the time the patient is first prostrated. Cases with intracerebral haemorrhage resulting from ruptured aneurysms may also show paralytic signs from the onset but not infrequently these do not become manifest for several hours and in about 25 per cent of our cases a period of one to twelve days elapsed before they developed.

If patients are conscious or a good history is available from friends, the extreme severity of the headache with its tendency to be posteriorly situated and the marked stiffness of the neck may also aid in the recognition of spontaneous subarachnoid haemorrhage. Consciousness frequently is retained in the presence of bloody cerebrospinal fluid in spontaneous subarachnoid haemorrhage whereas bloody cerebrospinal fluid in patients with primary intracerebral haemorrhage almost al-



ways indicates extension of the haemorrhage into the ventricles and is accompanied by deep unconsciousness and impending death. Therefore the preservation of consciousness at the onset favours the diagnosis of spontaneous subarachnoid haemorrhage but, as consciousness is lost in a large proportion of cases, this sign is of limited value only in differential diagnosis.

In the absence of hypertension, the occurrence of spontaneous haemorrhage, whether purely subarachnoid or mainly intracerebral, should always suggest a ruptured aneurysm as the probable basis. Gross haemorrhage occurring into the substance of a cerebral tumour and causing the sudden onset of signs of intracerebral destruction is not common. When it does occur it is not usually associated with blood in the cerebrospinal fluid. On the other hand, intracerebral haemorrhage due to the rupture of small aneurysms on the Circle of Willis is common and subarachnoid bleeding is present in a great majority of cases. Therefore, unless a case has features in the preceding history which are very suggestive of an underlying neoplasm, the diagnosis of haemorrhage into tumour should be made with great caution, particularly if there is blood in the spinal fluid.

We have been able to verify several cases of berry aneurysm with large intracerebral haemorrhages in which the associated subarachnoid bleeding was very slight, but we have not as yet encountered at autopsy a purely intracerebral haemorrhage from aneurysm. It is readily conceivable that an aneurysm deeply imbedded in the adjoining frontal or temporal lobe tissue might rupture directly into brain substance without leaving a trace of subarachnoid haemorrhage. This postulation may be considered almost verified by two of our fatal cases in which there was an initial subarachnoid haemorrhage with temporary recovery, then later a recurrence of bleeding entirely into cerebral tissue without further subarachnoid haemorrhage seen either by lumbar puncture or in the postmortem specimen.

Consequently, we feel that when a young or middle-aged person develops a sudden hemiplegia without obvious basis, such as hypertension, endocarditis or neurosyphilis, a ruptured berry aneurysm is the most likely explanation. If there is bloody cerebrospinal fluid the diagnosis is much more certain, but it remains a definite possibility even without subarachnoid blood. Cerebral haemorrhages, without hyper-

tension or arteriosclerosis, have been attributed to telangiectases in brain tissue, but our findings lead us to believe that imbedded aneurysms of the Circle of Willis are the most common cause of such cases. We have under observation three cases of this type. The ages are thirty-four, thirty and sixteen years respectively, and none has an abnormal blood pressure, syphilis or heart disease. All three suffered a hemiplegia of rapid onset. The cerebrospinal fluid was clear in two cases not examined in the third. In one of the cases with clear cerebrospinal fluid craniotomy was performed and a blood clot evacuated from the region of the internal capsule. Though we consider aneurysm the probable lesion in each of these three cases, this is by no means proven and the cases are not included in the series here reported.

Cerebral angioma has been recognized as a cause of repeated spontaneous subarachnoid haemorrhage (Vincent et al, 1938). It is rarely found in cases presenting themselves in adult life but probably accounts for the majority of cases in childhood when ruptured aneurysms are very uncommon. Angiomatous malformations are commonly surface lesions, and, although they do not usually give rise to haemorrhage, when they do so it is likely to be subarachnoid in situation. We have seen one such case with pathological verification. This patient died at the age of twenty-two in his third attack of subarachnoid haemorrhage from an arteriovenous angioma situated in the right cerebellar hemisphere, vermis and pons. The diagnosis of these cases from subarachnoid haemorrhage due to aneurysm can be readily made if a bruit is heard on auscultation of the skull. However, venous angiomas are not accompanied by a bruit and may be more difficult to diagnose. They usually produce symptoms in childhood, however, and may be associated with naevi on the face and congenital abnormalities of the ipsilateral eye which aid in their recognition.

In rare cases subdural haematoma may have to be considered, particularly when the onset of symptoms is gradual following some mild trauma. It is not common in subdural haematoma to have blood in the subarachnoid space and signs of meningeal irritation unless the trauma has been unusually severe. Although the onset in spontaneous subarachnoid haemorrhage may be gradual over a period of days, the history is shorter than that obtained in cases with subdural haema-

toma where it is frequently progressive over a period of weeks or months Merritt, 1938, has emphasized the value of spinal fluid pressure readings in differentiating these two conditions The pressure may be high in both but in subdural haematoma there is a marked fall in pressure with the removal of a small amount of fluid, while in spontaneous subarachnoid haemorrhage the drop in pressure is much more gradual This means of differentiation would not apply, however, in cases of ruptured aneurysms with intracerebral extravasation and it is these cases which are likely to give the greatest difficulty in distinguishing them from subdural haematoma Occasionally berry aneurysms on the Circle of Willis rupture directly into the subdural space with usually some subarachnoid bleeding also We have seen two such pathological specimens, both were rapidly fatal The possibility of such an occurrence must be kept in mind in certain cases where the symptomatology may be suggestive of both conditions

Occasionally cases of cerebral laceration following trauma have to be distinguished from ruptured aneurysm precipitated by trauma Both will show bloody cerebrospinal fluid and meningeal irritation In the absence of a demonstrable fracture of the skull, the diagnosis must be based on the clinical course of the patient Trauma sufficiently severe to cause laceration and haemorrhage is likely to be associated with cerebral concussion and the duration of unconsciousness may be longer than is usual with haemorrhage due to ruptured aneurysm The mental and emotional disturbance following recovery of consciousness will likewise be more severe if trauma to the brain is the basis of the haemorrhage

Large aneurysms may give rise to symptoms of gradually increasing intracranial pressure and in their effect on neighbouring structures they present a clinical picture which may be indistinguishable from a neoplasm Carotid aneurysms give a clinical syndrome that usually can be easily recognized but large aneurysms in other situations may show no distinctive symptoms Occasionally an aneurysm may be detected by X-ray, if it has calcium in its wall, as a rounded cystic shadow close to the sella A history of temporary exacerbation of symptoms in the presence of signs of subarachnoid haemorrhage, which can be attributed to a small leak of the aneurysm, aids in differentiation when it occurs The tumours which large aneurysms are most likely to

simulate are basal meningiomas, acoustic neuromas and pituitary adenomas. A pituitary adenoma can usually be readily distinguished from an aneurysm by the enlargement of the sella and the erosion of its floor. Jefferson, 1937, has drawn attention to the difficulty of differentiating certain anterior cerebral aneurysms which are exerting pressure on the optic chiasma, and pituitary adenomas with or without sudden haemorrhage into the latter. He points out that with an aneurysm in that situation the inferior temporal visual fields tend to be affected first, whereas an adenoma will cause change in the superior temporal fields in the early stages. In late cases with complete hemianopia the only means of differentiation may be by the history, in the case of an aneurysm of a sudden onset with pain and perhaps oculomotor palsies. It must be considered that a suprasellar tumour, either meningioma or cyst, is likely to affect the visual field similarly to an aneurysm. In that event the X-rays might help in differentiation, although in certain instances the changes in the sella and the situation and amount of calcification are not sufficiently characteristic to definitely establish the diagnosis. Here again angiography with thorotrast may be of great aid in diagnosis.

### *Prognosis*

*Immediate Prognosis* There are a number of factors during an attack of spontaneous subarachnoid haemorrhage due to ruptured aneurysms which have a bearing on the prognosis. It has been shown that approximately 50 per cent of the patients seen during the acute phase of the condition recover. Predictions as to which cases will recover and which will not are subject to considerable error due, in part, to the impossibility of foretelling the likelihood of further bleeding. However, the statistics which we have presented enable a few generalizations to be made.

*Age of the Patients* It has been shown that mortality tends to be greater in the higher age groups. Thus, the average age of the fatal cases was ten years higher than that of the survivors. However, advanced age does not preclude recovery even when severe haemorrhage is present. The oldest survivor in this series was aged seventy-two.

*Underlying Disease* Strauss and Tarachow, 1937, have found a high incidence of underlying disease in their cases of spontaneous

subarachnoid haemorrhage. They suggest that the prognosis is the prognosis of the underlying disease. Our experience does not conform with theirs and the great majority of our patients were enjoying good health at the time the haemorrhage occurred and had no evidence of any underlying disease on examination. The only condition which was found with sufficient frequency to render it significant was a preexisting arterial hypertension which was present in sixteen cases (13 per cent). Ten of these were fatal (62 per cent), suggesting that the presence of hypertension tends to a poorer prognosis in a case of subarachnoid haemorrhage.

*Circumstances of Onset* Our observations indicate that the activity of the patient at the time the haemorrhage occurred was of little importance in determining its onset or severity. The great majority of patients were engaged in their ordinary routine or were in bed asleep when symptoms first became manifest. A relatively small proportion were indulging in some unusual exertion or had been subjected to recent trauma. The mortality was not essentially different in the two groups. There is a suggestion, however, that a patient under the necessity of continuing activity following the onset of symptoms is likely to increase the severity of the haemorrhage. This was illustrated in the following case. A healthy young girl, who was swimming at the time of onset, signalled distress to her sister on shore but the latter did not take the matter seriously. Unable to get assistance, the patient struggled to shore and collapsed on the beach unconscious. Death occurred two hours later and autopsy showed an unusually massive subarachnoid haemorrhage due to a ruptured aneurysm.

*Loss of Consciousness* When this occurs at the onset, or more commonly shortly afterwards, the outlook is a little worse than in cases without loss of consciousness. Of the sixty patients in our series who lost consciousness early in the illness, 62 per cent progressed to a fatal termination. It would seem that in general the longer the period of unconsciousness the worse the prognosis. However, this does not hold true in all cases because five of our patients who survived were unconscious from one to eight days.

*Gross Involvement of Cerebral Tissue by the Haemorrhage* This complication makes the prognosis a little worse but not so much as might

be expected. The mortality rate in spontaneous subarachnoid haemorrhage without evidence of cerebral damage was 47 per cent, whereas with neighbourhood signs it was 55 per cent. If cases showing only cranial nerve paralysis are eliminated from this latter group, the mortality becomes higher, namely 60 per cent. One might anticipate a higher mortality than this in the sixty-two cases with signs of gross extravasation into the hemispheres, in view of the much higher mortality that occurs with primary intracerebral haemorrhage. However, with ruptured aneurysms the degree of cerebral extravasation is determined principally by the relationship that the site of rupture bears to the cerebral tissue. Its occurrence is no indication that the haemorrhage is unusually large or grave.

There are several reasons why the prognosis is better in cases with intracerebral haemorrhage due to ruptured aneurysms than in those with primary intracerebral haemorrhage. The latter is practically always associated with hypertension and cerebral vascular disease and it has been shown that patients, on the average, are older and would therefore have less recuperative capacity. Also with primary intracerebral haemorrhage there is likely to be much more severe and rapid destruction of tissue than with haemorrhage due to ruptured berry aneurysms. In the latter the force of the haemorrhage is lessened because the source of bleeding is commonly in communication with the subarachnoid space and a partial escape usually occurs by this route.

*Summary* Approximately 50 per cent of the cases recover. Therefore the prognosis is much better than in primary intracerebral haemorrhage. In a given case however, the immediate prognosis may be difficult to assess unless the haemorrhage is very mild or very severe. This is largely due to the possibility that the bleeding will continue or recommence. In the majority of cases there is no evidence of any underlying disease so that this is not of much assistance in making a prognosis. The presence of hypertension however makes the prognosis a little poorer and the mortality is a little greater in the older age groups. Unconsciousness at the onset is not necessarily of bad prognostic significance unless it is prolonged. The circumstances at the time of onset do not significantly affect the prognosis unless the patient is required to make strenuous efforts after the haemorrhage.

has started Extension of haemorrhage from ruptured aneurysms into cerebral tissue favours a poor prognosis but not by any means so bad as in primary intracerebral haemorrhage

*Ultimate Prognosis* In November, 1938, we endeavoured to make contact with all the surviving patients in this series As a result of this follow-up we are able to report on the developments subsequent to discharge from hospital in thirty-seven (63 per cent) of those patients surviving the initial illness Twenty-eight of these were re-examined by us, letters were received from seven describing their present status, and the remaining two died in the interval

Table 5 summarizes the findings in these thirty-seven patients As would be expected, there is a much higher incidence of patients free

TABLE 5

*Present Status of 37 Cases of Spontaneous Subarachnoid Haemorrhage*

Discharged from hospital 1928-1938, re-examined 1938-1939 The time between hospital admission and re-examination varied from 6 months to 10 years, with an average of 4 years

	WELL	MILD RESIDUAL SYMPTOMS	SEVERE RESIDUAL SYMPTOMS	RECURRENCES OF HAEMORRHAGE	DIED
With neighbourhood signs (27 cases)	4	14	8	3	1
Without neighbourhood signs (10 cases)	8	1	0	2	1

of symptoms in the group with uncomplicated spontaneous subarachnoid haemorrhage but the majority of the twenty-six patients with signs such as hemiplegia, aphasia, hemianopia, etc, while in hospital, have shown a marked degree of recovery from the severe disability present at the onset There remain only six survivors showing signs of cerebral involvement by the haemorrhage during their attack who were not followed up On discharge, three of these were almost free of symptoms, the other three showed gross intellectual impairment, optic atrophy and hemiparesis respectively

Our experience indicates that a patient who recovers from an attack of spontaneous subarachnoid haemorrhage without neighbourhood signs will, in all probability, suffer no permanent residual

symptoms Where complete cranial nerve paralysis, usually oculomotor, is the principal or only neighbourhood sign recovery of the function of the nerve is likely to be incomplete but in mild partial paralysis there may be no permanent disability Cases with signs and symptoms of haemorrhage extending into the hemispheres may present a difficult problem in prognosis It is frequently impossible to predict how much recovery will occur until the patient has been observed for several weeks or even months Patients with evidence of marked cerebral involvement in the early stages may show a remarkable degree of recovery, whereas those with apparently less severe signs may be left with residual disability The symptoms due to subarachnoid haemorrhage sometimes mask the manifestations of cerebral damage at the onset and prognosis should always be guarded until the patient is sufficiently cooperative that the clinical findings and progress can be correctly evaluated

As previously described, we consider that residual signs of hemisphere lesions (paralysis, dementia, aphasia and hemianopia), are accounted for by "meningocerebral" haemorrhage Another explanation offered for persistent focal cerebral signs after subarachnoid haemorrhage is thrombosis of the artery from which the aneurysm arises This was seen in one of our autopsy cases and was presumed to occur in one non-fatal case It has been reported by other observers Enzer and Schwade, 1937, reported a case, verified at postmortem examination, with thrombosis of the right middle cerebral artery attributed to a ruptured aneurysm They stress the importance of thrombosis in cases of ruptured aneurysm as a cause of increasing symptoms, despite demonstrable improvement in the cerebrospinal fluid Jefferson, 1937 has also emphasized the relationship of posterior cerebral arterial thrombosis to an aneurysm pointing out that aneurysms of the limbs commonly predispose to thrombosis However, if thrombosis is a common aftermath of ruptured intracranial aneurysms it should be seen more often at postmortem examinations Its infrequency, as compared with extravasation of blood into cerebral tissue, indicates that the latter is a much more common cause of permanent disability following rupture of aneurysms

*Multiple Attacks of Spontaneous Subarachnoid Haemorrhage* A very important consideration in prognosis in spontaneous subarachnoid



haemorrhage is the question of the liability in any given case to subsequent attacks. In this series multiple attacks were comparatively infrequent. We have considered as cases with multiple attacks only those where there has been a definite remission of at least two months between the recovery from one attack and the onset of another. Exacerbations of bleeding, while under observation in hospital, are common and have been regarded as recurrences of the same haemorrhage before healing has taken place and not as separate attacks of haemorrhage.

A history indicating that a previous attack of spontaneous subarachnoid haemorrhage had occurred was obtained in eleven of the 118 cases on admission to hospital. In the follow-up of thirty-seven surviving patients, it was found that only five had suffered attacks subsequent to the one which brought them under observation. Of the sixteen patients known to have had multiple attacks, three are dead and eight are known to be alive at the present time. Death in these three instances was due to spontaneous subarachnoid haemorrhage.

Four attacks were the maximum number recorded in this series as occurring in one individual. Each of three patients has suffered four attacks. Three other cases each had three attacks and the remaining ten each had two. The longest remission between two attacks in one individual was eleven years and, in the majority of cases, the interval between attacks was more than five years. The average interval in the three fatal cases between the initial attack and the attack in which they died was five and a half years. The average period since the initial attack in the eight survivors, who are at present under observation, is approximately seven years.

It is not easy to obtain any clear idea as to what factors predispose an individual to multiple attacks. Age does not seem to be important because in this group the ages varied from twenty to sixty-five years. Only three of the sixteen patients had hypertension, giving an incidence approximately the same as in those cases not having multiple attacks. A consideration of the patient's occupation does not indicate a greater liability to multiple attacks in those engaged in strenuous work. The severity of the initial attack is no index of the liability to further attacks. Patients have been followed after an extremely severe course in hospital with repeated exacerbations of bleeding and on recovery they have carried on their ordinary activities for years.

without recurrence. On the other hand several of the patients with multiple attacks had relatively mild initial illnesses and with the subsequent haemorrhages were much more seriously ill

It seems probable that a competent walling off by adhesions at the site of rupture will render future attacks less likely to occur. It is possible that this takes place more effectively in a severe attack particularly if the patients are not allowed to resume activity too soon and receive a period of rest at the time of their attack sufficient for adequate healing to occur. The treatment employed will be considered in detail in the next section, and it undoubtedly is an important factor in prognosis. Ayer 1934 has suggested that spontaneous cure of aneurysms may take place by thrombosis of the sac. This might occur without rupture but it is reasonable to suppose that, after rupture and the formation of a clot at the site thrombosis of the aneurysmal sac is rendered more likely. Strauss and Tarachow 1937, have suggested that a proved or presumptive history of previous attacks makes the prognosis of the presenting attack better. Our figures would tend to support their opinion because the mortality in all cases was 52 per cent whereas the mortality in the cases with multiple attacks was only 17.5 per cent. Although there are obvious sources of error in these figures as they are not complete it is at least justifiable to conclude that the mortality is no greater in subsequent ruptures than in the initial haemorrhage.

*Summary* The ultimate prognosis is good in cases recovering from pure spontaneous subarachnoid haemorrhage the patients usually having no residual symptoms. Even where evidence of cerebral involvement by the haemorrhage is present the majority of patients recover with little residual disability. Gross destruction of cerebral tissue is the commonest cause of severe signs which are permanent and much less commonly, thrombosis in an artery upon which the aneurysm is situated may cause permanent damage. Multiple attacks were not common in this series and it would seem that their danger has been overemphasized.

### *Treatment*

The most important factor in treatment is complete rest in bed. In an uncomplicated case without exacerbations of the haemorrhage the period of rest should not be less than six to eight weeks. Patients

with hypertension should probably be kept at rest for somewhat longer periods. In many instances where recurrence of the bleeding occurs even while patients are at rest, it will be necessary to keep them in bed for a considerably longer time. No patient should be allowed up until free of such symptoms as headache, stiff neck, vertigo, etc. for at least four weeks. The importance of this cannot be overestimated. Some patients improve very rapidly following admission to hospital and it is a temptation to yield to their request that they be allowed up. To do so, however, may result in serious consequences as in the following case.

A man, aged 31, was admitted to hospital on January 29, 1934, with the history of a sudden pain in the back of the neck a few hours before while working, followed shortly by nausea, vomiting and collapse. Examination showed the neck to be stiff but no other physical signs. The cerebrospinal fluid contained gross blood. Daily lumbar puncture was done with removal of small amounts of bloody fluid. By February 1 the fluid was free of blood and the patient feeling very much improved. He was allowed to return home on February 10, as he was entirely symptom-free and examination was negative. On February 12 he was out walking during a storm when he suddenly collapsed and died within thirty minutes. Postmortem examination showed severe subarachnoid haemorrhage, mainly at the base due to the rupture of an aneurysm on the basilar artery.

It is reasonable to suppose that if this patient had been kept at complete rest until organization of the clot at the site of the rupture was complete, he probably would have suffered no recurrence of his haemorrhage when allowed to resume ordinary activity. The interval necessary for organization to occur cannot be estimated accurately but it is probable that it would require not less than four weeks following subsidence of the haemorrhage and it would seem safer to allow six to eight weeks to elapse before commencing even moderate activity. When it is deemed safe to allow patients up, the return to ordinary activity should be very gradual and any strenuous exertion avoided for at least four months after the bleeding has stopped.

The patient should receive good nursing care during the acute phases of his illness and can be treated best in hospital. The head of the bed should be elevated to aid in reducing the increased intracranial pressure. Good nursing can do much to allay restlessness but

the judicious use of sedatives is usually necessary. We have found codeia and aspirin quite satisfactory for the relief of pain in most cases. Bromide and chloral or phenobarbital are of great aid in controlling restlessness and irritability and in promoting sleep. The bowels should receive very careful attention. The patient should be warned at the outset to avoid straining on the bed-pan. One of our cases who had passed the acute stage and was apparently recovering, died suddenly from recurrent haemorrhage while on the bed-pan. Liquid paraffin administered several times a day with a small enema every two days, if necessary, is usually sufficient. The intravenous administration of hypertonic solutions appears to be of value in certain severe cases who remain comatose, by permitting a temporary improvement in the cerebral circulation through a lessening of the oedema.

The subject of spinal drainage in these cases has given rise to considerable controversy. Ayer, 1934, strongly opposes repeated drainage of the bloody cerebrospinal fluid on the grounds that the reduction in pressure may interfere with the processes of healing at the site of rupture and lead to further bleeding. Merritt, 1938, on the other hand, states that the danger from drainage has been overemphasized. He advocates removal of sufficient bloody fluid to bring the pressure to normal twice daily for the first few days and once daily thereafter until the fluid is clear. One of us (Hyland), writing on this subject in 1933, advocated daily spinal drainage with very slow removal of the fluid. However, subsequent experience has made us question this method of treatment because we do not believe it is without danger and its value remains to be proven. We have attempted to evaluate the efficacy of spinal drainage in the treatment of spontaneous subarachnoid haemorrhage by making a survey of forty-nine of the surviving cases in this series. Twenty-six of these patients had from four to twenty lumbar punctures with withdrawal of from ten to thirty cubic centimetres of cerebrospinal fluid on each occasion, at sufficiently close intervals to be termed treatment by spinal drainage. The remaining twenty-three cases had from one to four lumbar punctures each with removal of smaller amounts of cerebrospinal fluid at longer intervals for the purpose of diagnosis, relief of symptoms and estimation of progress.

Thirty of the forty-nine cases have been followed to date. Four-

teen have remained symptom-free with no residual signs and no recurrence of haemorrhage for periods up to seven years. Six of these were treated by spinal drainage and eight were not. Four of the other sixteen patients had subsequent recurrences of haemorrhages, two having been treated by repeated drainage and two not having received this treatment. The twelve remaining cases showed residual signs or symptoms of varying severity, namely—headaches, psychoses, mild dementia, ocular paralyses, convulsion, paresis of limbs and aphasia. Six of these had been treated by drainage and six had not. There was no evidence that the nature of the residual symptoms bore any relation to the administration or to the withholding of this treatment. Of the two cases with severe psychoses which persisted following the haemorrhage, one received seventeen spinal drainages but the other was not treated by drainage. Both cases with mild dementia following the attack received spinal drainage.

The above figures tend to substantiate the clinical impression which we have gained that spinal drainage in cases of spontaneous subarachnoid haemorrhage is not an essential part of the treatment. There was no evidence obtained that drainage lessens the mortality, tendency to recurrence, or the residual symptoms after recovery from the haemorrhage. There are, however, certain cases in which removal of a moderate amount of bloody fluid causes immediate and marked relief in the symptoms and where repetition of the procedure seems to shorten materially the duration of the acute symptoms. Its use as a method of treatment should probably be confined to cases of this sort and not as a routine method of treatment. Cases sometimes become worse following drainage, due, no doubt, to increased bleeding as a result of the reduction in pressure before proper organization of the clot had occurred at the site of the rupture. For this reason, if drainage is decided upon, the fluid should be removed slowly and in small quantities. Any sudden drop of pressure is an indication to stop the procedure at once. As a result of Bagley's (1928) work on the effects of experimental subarachnoid haemorrhage in dogs, it has been considered a possibility that meningeal adhesions and cortical damage might follow if the foreign blood in the cerebrospinal fluid was allowed to remain. Pathological and clinical experience in the human does not support this view and the indications are that the

breakdown products of haemoglobin can be adequately dealt with in the subarachnoid space

In summing up, we believe that in a given case lumbar puncture should be carried out on admission for diagnosis and subsequently if any exacerbations of symptoms occur. Relatively small amounts of fluid should be removed slowly on each occasion. If a patient is showing progressive improvement, there is no justification for carrying out spinal drainage. In certain cases where the patient has obtained immediate and marked relief after the first puncture and subsequently appears to remain stationary with persistent symptoms, the procedure may be repeated cautiously. The fact that it confers no ultimate benefit on the patients and that it is not without danger, renders it inadvisable as a routine procedure.

*Surgical Treatment of Aneurysms* Formidable difficulties have been encountered in attempts to treat berry aneurysms directly by surgical excision or by ligation of the carotid artery. Angiography with thorotrast usually enables localization of an aneurysm, but is a procedure not entirely free from danger. Dandy (Matas, 1938) has successfully tied off the neck of an aneurysm without ligating the artery in one case. This procedure, though ideal, must rarely be feasible because of the tendency for the aneurysms to be attached by a very short neck to large arteries. The simpler operation of ligating the carotid artery in the neck has been found of value in some cases. The results obtained are variable and unpredictable because of our very limited knowledge of collateral circulation in the brain. The relative infrequency of recurring leaks from aneurysms, in this series, suggests that arterial ligation should seldom be considered as a means of preventing later haemorrhages. Surgical efforts should probably be restricted to the larger aneurysms causing local pressure symptoms.

The danger of causing cerebral infarction, when the carotid artery is ligated, can be estimated, and usually prevented, by preliminary repeated compression of the artery, as in the following case.

*Case 10* H. B., a domestic, aged 33, was admitted to hospital on February 18, 1938. She had been well until October 24, 1937, when she was awakened during the night with very severe pain in the right occipital region accompanied by vomiting. The pain lessened in severity after

about fifteen minutes but on the following day, she suffered from a persistent pain in the right frontal region, chiefly localized behind the right eye, which continued up to the time of admission to hospital. On October 26, two days after the onset of pain, she suddenly developed ptosis of the right upper eyelid and double vision on opening the lid with her finger. This condition remained unchanged until admission but the pain behind the right eye became considerably less severe. Examination showed a complete paralysis of the right third nerve. No other abnormal findings were detected. The cerebrospinal fluid was 100 mm and apart from a faint yellow tint, it was negative.

**Diagnosis** An aneurysm situated on the right internal carotid artery.

On February 23, 1938, 20 c.c. thorotrast were injected into the right common carotid artery. X-rays revealed a rounded shadow, measuring about 1 cm. in diameter, situated lateral to the sella turcica. This was presumed to be an aneurysm arising from the right internal carotid artery.

From March 15 to April 25, 1938, daily digital compression of the right common carotid artery was carried out, gradually increasing the period of compression. At first the patient complained of some paraesthesia in the left upper limb but after a few days this ceased to occur with the compression and finally the artery could be compressed for forty-five minutes without the patient experiencing any symptoms. On April 25 a clip was placed on the right common carotid artery with no ill-effects and the patient subsequently was discharged from hospital. She returned on July 7, 1938, and stated that she had had no headache whatever since discharge. The ocular paralysis was unchanged. Under local anaesthetic, the right internal carotid artery was tied off. Shortly after this procedure, the ocular paralysis commenced to improve and by January, 1939, the ptosis had completely recovered and the power of the extrinsic and intrinsic ocular muscles had returned almost to normal.

In this case, the onset of the third nerve paralysis was not accompanied by any severe spontaneous subarachnoid haemorrhage. The aneurysm was demonstrated by angiography and appeared to be situated at the carotid bifurcation, probably closely applied to or even adherent to the third nerve. In our experience aneurysms of the internal carotid artery are more common in this situation than in the cavernous sinus where the sixth and fourth nerves would probably be affected equally with the third.

The data available are not sufficient to assess accurately the value of extracranial ligation but it is assumed that the reduction of pres-

sure, which occurs in the aneurysm following the cessation of blood flow through the internal carotid on that side, may result in the relief in pressure symptoms and protect the patient against subsequent rupture of the aneurysm

#### SUMMARY AND CONCLUSIONS

Clinical and pathological observations based on 118 cases of spontaneous subarachnoid haemorrhage and eight large unruptured aneurysms causing local pressure have been presented. The pathological material also included nine cases of unruptured aneurysms found only at autopsy.

Ruptured aneurysms of the Circle of Willis and of the proximal part of its branches accounted for the vast majority of the fatal cases of nontraumatic subarachnoid haemorrhage. In thirty-four of such cases, a ruptured berry aneurysm was found in twenty-seven, and an angioma in one. In the other six cases there had been an apparent rupture of an artery at the base of the brain but no bleeding point was found. Four of these cases occurred in the earlier half of the eleven-year period of this review and it is likely that a careful search for aneurysm may not have been made. In the past five years, when a more meticulous dissection of the arteries was carried out, only two of twenty-four cases failed to yield an aneurysm. In those two cases no other cause was found and there may have been aneurysms hidden or blown off by the massive haemorrhages.

At autopsy fifty-three aneurysms were studied in forty cases. Fifty-one of these aneurysms were rounded and saccular, occurring at bifurcations. They are of the type considered developmental in origin, but as we do not feel the proof of this aetiology to be conclusive, we have preferred the term "berry aneurysm". They were associated either with healthy vessels or with varying degrees of arteriosclerosis. There were two cases of fusiform aneurysm of the basilar artery which were thought to be definitely caused by arteriosclerosis. The histological findings of the aneurysm walls have been described.

Points of bifurcation of middle cerebral and basilar arteries were studied histologically in seven cases of various ages without aneurysms and in one case with an aneurysm on another cerebral artery.



Five of the eight cases showed medial defects, as described by Forbus, 1930, and in two cases there were microscopic aneurysms. No contribution to the aetiology of berry aneurysms can be made from this work. We believe that the medial defects are probably developmental and play a part in causing aneurysms, but that there is another unrecognized acquired lesion which causes degeneration of elastic tissue.

In examining the brains of cases of fatal aneurysmal haemorrhage, we were particularly impressed by the frequency of intracerebral haemorrhage, often of large size, and in some cases greater than the subarachnoid haemorrhage. Such intracerebral ruptures tend to occur from a berry aneurysm which is nesting in the adjoining cerebral cortex, and there was frequently a preceding subarachnoid haemorrhage. These haemorrhages occurred primarily into temporal and frontal lobes from aneurysms at the carotid bifurcation, on the middle cerebral artery, or on the anterior cerebral and communicating arteries.

The frequency, age, and mortality of primary arteriosclerotic intracerebral haemorrhage have been compared with those of spontaneous subarachnoid haemorrhage over the same eleven-year period. There were 148 cases of primary intracerebral haemorrhage and 118 cases of spontaneous subarachnoid haemorrhage. Autopsies were performed on thirty-three cases of massive nontraumatic subarachnoid haemorrhage, and sixty-seven cases of primary intracerebral haemorrhage in the same period. The mortality of intracerebral haemorrhage was 88 per cent (as nearly as could be determined), and of subarachnoid haemorrhage 52 per cent. It is of interest that massive intracerebral haemorrhage from berry aneurysms, or meningocerebral haemorrhage, was found in nineteen autopsy cases.

The average age of the cases of spontaneous subarachnoid haemorrhage was forty-six, with 60 per cent under fifty. In primary intracerebral haemorrhage the average age was fifty-nine, with 70 per cent over the age of fifty.

Surviving and fatal cases have been reported which illustrate the clinical syndromes of aneurysmal rupture, such as spontaneous subarachnoid haemorrhage, cranial nerve involvement, and hemiplegia, hemianopia and aphasia, from intracerebral haemorrhage. Cases in

this latter group have been stressed to show the pathological correlation of the clinical syndromes of temporal and frontal lobe haemorrhage from aneurysms. Case 4, a young man with hemiplegia and aphasia, is particularly impressive in that a calcified aneurysm could be seen and it was possible to observe a progressive dilatation of the left lateral ventricle by three encephalograms in a four-year period. Cases 5 and 6 are similar cases of temporal lobe haemorrhage, with fatal outcome and pathological verification. Frontal lobe haemorrhage with dementia is illustrated by Case 7. Two unusually large aneurysms causing tumour symptoms have been reported. One of these presented a cerebellopontine angle syndrome, and the other had a prolonged dementia from frontal lobe compression.

The clinical features of the cases of subarachnoid haemorrhage have been surveyed in some detail with reference to preceding disorders, nature of onset, localizing signs, ophthalmoscopic findings, cerebrospinal fluid changes, and multiplicity of attacks. Diagnosis, prognosis and treatment have been discussed in the light of our own observations.

Hypertension was the only constitutional disorder preceding attacks of subarachnoid haemorrhage with sufficient frequency to be considered of significance. In sixteen cases there was known pre-existing vascular hypertension. In only four cases was there a history of migraine, so that we were unable to substantiate that relation between migraine and intracranial aneurysm which has been postulated. There was only one case of neurosyphilis and one case of diabetes mellitus in the series. The majority of cases had no symptoms preceding the onset of haemorrhage. Fourteen patients had suffered headaches over a long period, and eight had attacks of vertigo. A preceding intellectual deterioration for longer than one year was present in three cases, and two of these suffered a fatal rupture of an aneurysm in the region of the anterior communicating artery. Trauma bore a possible relationship to the onset of spontaneous subarachnoid haemorrhage in ten cases. In four cases a mild head injury had occurred within one week, and four patients had suffered severe head injuries from one to six months previously.

In 108 cases, where the information was available, the haemorrhage began during strenuous exertion in only fourteen. Fifty-five cases

had their onset during ordinary activity, and sixteen began during sleep or on awakening. Three patients suffered their attacks immediately after mild trauma. There was a surprisingly high incidence of unconsciousness, which occurred in twenty-nine cases with the onset, and in thirty-one cases soon after the onset. Convulsions occurred in only 9 per cent of the cases. The usual onset was one of sudden, severe headache. Transient signs such as mental confusion, sluggish pupillary reactions, sluggish or absent tendon reflexes and extensor plantar responses occur often, followed by complete recovery, and are probably due purely to subarachnoid bleeding. Cranial nerves were affected in eighteen cases of spontaneous subarachnoid haemorrhage, the third nerve was most frequently involved.

Hemiplegia, monoplegia, aphasia, hemianopia and hemianaesthesia, singly or in combination, were encountered in sixty-two cases with spontaneous subarachnoid haemorrhage. In nineteen of these there was postmortem verification, showing that the usual cause of such focal cerebral signs was gross haemorrhage into cerebral tissue from an aneurysm of the Circle of Willis. The clinical findings correspond with the high incidence of rupture into cerebral tissues encountered in the total postmortem specimens of fatal aneurysmal rupture. The case reports include cases in which such signs of intracerebral haemorrhage were of much greater prominence than the manifestations of meningeal haemorrhage. We have also mentioned three cases of sudden hemiplegia due to intracerebral haemorrhage in young non-hypertensive persons, with the suggestion that they are probably caused by ruptured berry aneurysms. The clinical syndromes, produced by temporal and frontal lobe haemorrhages from berry aneurysms, have been discussed.

Prognosis in spontaneous subarachnoid haemorrhages has been considered in detail. The immediate prognosis in an individual case may be very difficult. The outlook is a little worse in older persons or in those with a preceding hypertension. The mortality is only a little greater in those who lose consciousness at the onset, but several cases with deep or prolonged unconsciousness have survived. Signs of intracerebral bleeding, such as hemiplegia, aphasia and hemianopia, make survival a little more uncertain. If there has been one or more preceding attacks, the prognosis is no worse and possibly is

a little better. The ultimate prognosis in a surviving case of pure subarachnoid haemorrhage is good, and such cases commonly have no sequelae. A case with complete hemiplegia, hemianopia, severe aphasia or dementia will retain these signs to some degree, but incomplete lesion often show complete recovery. Thirty-seven cases have been followed from one to eleven years after their haemorrhage and the results are tabulated. Eleven are perfectly well, fifteen have mild residual signs, eight have severe residual signs, and two have died. Only five of these patients had suffered recurrences of haemorrhage.

Two or more attacks of spontaneous subarachnoid haemorrhage are known to have occurred in only sixteen cases (14 per cent), and the greatest number of attacks suffered by one individual was four.

Treatment of spontaneous subarachnoid haemorrhage is, primarily, complete rest aided by careful nursing and sedation. We have found no essential difference in the outcome of cases treated with and without repeated spinal drainage, and we believe lumbar punctures should be done only for diagnosis, and then as indicated for relief of symptoms.

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# PERIODIC PARALYSIS<sup>1</sup>

## A CLINICAL SYNDROME

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### INTRODUCTION

Paroxysmal palsy of the skeletal musculature may be identified from the prototype familial periodic paralysis. The condition is recognized clinically by the development of intermittent attacks of flaccid paralysis of the muscles of the extremities, loss of deep reflexes and loss of excitability to electrical stimulation of nerves and muscles. There is no impairment of mental faculties. The etiology

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of the paralysis is probably functional in so far as no gross anatomical changes may be demonstrated regularly in the spinal cord, peripheral nerves or affected muscles

An exhaustive survey of the literature on periodic paralysis constitutes the basis for this review. The bibliographic investigation was considered to be desirable in order to construct a more satisfactory definition of the clinical picture than has been presented heretofore in current literature. During this pursuit it occurred to us, as it has occurred to others previously, that periodic paralysis is a syndrome rather than a disease entity and that the familial type may be but one of several. This opinion was expressed admirably by Taylor (88) in 1898. "The term family periodic paralysis is purely clinical and descriptive, and should be definitely understood. If through a certain poverty of words we occasionally speak of the symptom-complex under consideration as a disease, it is merely as a matter of convenience, and in no way is indicative of a dogmatic belief that a periodic paralysis, as such, can itself represent a pathological entity. Our feeling, rather, is that we are dealing here merely with a symptom, or symptoms of extraordinary constancy, whose etiology and pathological anatomy, are as yet wholly obscure."

We are in agreement with this sentiment and believe that evidence is available now to support it. A separation and allocation of cases of periodic paralysis into more than one category was suggested first by those cases which appeared sporadically as opposed to those which appeared in families in which other members were afflicted also. It was noted, further, that some patients suffered attacks of paraplegia following bouts of malaria, others experienced similar difficulty in association with enlargement of the thyroid. A recently discovered link in the chain of evidence which supports Taylor's contention has been derived from the study of Addison's disease. Following excessive assimilation of desoxycorticosterone acetate during the treatment of patients with adrenal insufficiency, attacks of temporary paralysis of the skeletal musculature have been observed. It is of interest that the clinical picture of periodic paralysis which is induced by overtreatment with this synthetic hormone is not unlike certain other types of paroxysmal palsy.

## PLAN OF PRESENTATION

The presentation of the several aspects of periodic paralysis follows the orthodox plan. Throughout the review, it is assumed that the pathogenesis of periodic paralysis is uniform irrespective of the etiologic factor or factors which serve as inciting agents. Although experimental proof for this assumption is incomplete, clinical evidence substantiates it. In the section on Nosography, a liberal interpretation of the clinical syndrome is adopted. In the discussion of Incidence, unless otherwise stated, reference will be restricted to patients with hereditary periodic paralysis or sporadic paralysis not associated with a complicating disease such as malaria. In the other sections, particularly that of Clinical Description, strict adherence to the recognized familial type is maintained. This seemed desirable because the number of cases of familial periodic paralysis comprise a majority of the total cases of periodic paralysis of all types that have been investigated with meticulous care and reported.

Studies of the constituents of the blood and urine have been made on few patients with periodic paralysis. Notably lacking in this respect are studies on patients with the paralysis which is associated with malaria and thyroid dyscrasias. Complete metabolic studies of intake and output are rare, some which we have made on a patient with sporadic periodic paralysis are presented under Laboratory Studies. A case report of this patient is appended.

## DEFINITION

Periodic paralysis is a good descriptive appellation and will be used in this discussion for the symptom complex. Other terms which have been employed in the past include paraplegia spinalis intermittens nervosa, Shakhnowitsch (83), nocturnal paralysis, Fere (24), night palsy, Mitchell (57), exhaustion paralysis, malarial paraplegia, Suckling (172), paroxysmal paralysis, paroxysmal myoplegia, Kirk and Moller (133), periodic spinal paralysis, Oddo-Audibert paralysis, asthenia paroxysmalis Bornstein (101), myatonia periodica Kulneff (49), parental periodical paralysis, Booth (11), periodic family paralysis and familial periodic paralysis. The employment of eponymic terms for the syndrome is disapproved because of the difficulty of

deciding who described the malady originally. There are two criticisms against allowing the term family periodic paralysis to assume generic significance. Many cases of periodic paralysis appear sporadically and not in families. Secondly, it is preferable to designate such afflictions which may be transmitted from parent to child as hereditary rather than familial. The disease entity "paraplegie familiale spasmodique" of the French, [Marnesco (205)] or heredo-cerebral ataxia is not to be confused.

#### NOSOGRAPHY

Contemporary literature ascribes to Cavaré (107) the first description of periodic paralysis. The patient reported in 1853 by the French clinician was a 24 year old female who suffered from attacks of general paralysis of from 5 to 8 hours duration. No reference is made to a concomitant malarial infestation, but this seems likely because the patient had a quotidian type of fever which subsided as did the attacks of paralysis with quinine medication. There are other reports of periodic paralysis earlier in the nineteenth century than this but these are antedated by a century by a clear-cut description given by Musgrave (148) in 1727. His complete report without revision is as follows.

In Aug 1687 I was desir'd by a poor Woman, at *Astrop-Wells*, to look on her Daughter. They came from *Stow* in *Gloucestershire* (as they had often done before) for Work. The Daughter was about 21, of a Sanguine Complexion, and as to private matters well enough. She had been for several Days less active than usual and after that, had (a Week before I saw her) lost her Speech, and the use of her Legs, she had little or no sense of Feeling in them, and the Left Leg was drawn up as in a violent Cramp. Her Ruddy Sanguine Look directed Bleeding, but that did not relieve her. I then gave her *Spirit of Sal Ammon Succinated*, Steel with Gentian, Amber, Castor, and other warm Cephalicks. A Blister was laid on her Neck. A Bath of (Wormwood, and other hot Herbs) prepared for her Legs, *Ung, Marthatum* used to anoint them after Bathing. By these Means, she was, in the space of 3 Days, able to speak again, and in a little time, by the help of Crutches, able to go. But then omitting the Medicines, tho' but one Day, she lost her Speech again, and returning to them (especially the Spirit) recover'd it as soon. When not able to speak, she had a manifest Alteration

in her Face, the Strength and Tonick Vigor of it abated, her Eyes grew dull, her Lips pale I have, in this Juncture, given her 30 Drops of the Spirit, In the space of two Hours the change has been surprising, her Eye has quicken'd, a Colour came over her Face, her Speech return'd

In *July* 1688, her Mother brought her to me again, and told me, That after the Physick, I had (the Year before) prescrib'd her, was all spent, her Speech, and the Use of her Legs left her first in *September*, on a *Tuesday* about Noon, and return'd the *Saturday* following near the same Hour, and that from *Michaelmas* to the Time of our discourse (which was *July* 18, following) her Speech and Strength of Legs observed the same Period (of going off on *Tuesdays* every Week, and returning on *Saturdays*) with only two Exceptions, *viz* That once they returned on a *Friday*, another time not before *Sunday* She added, That her Daughter was, the preceding Winter, very weak, and in danger of Death, that her Appetite was much abated, that she sometimes chose to eat Bread, Water and Salt, boil'd together, that now, as the Summer came on, she recovered some degree of Strength, that she had lost no Sense at any Time, besides that of Feeling, which was by the first Quantity of Medicine restored effectually, and without Relapse That the Menses were regular as to Period, but as to Quantity unequal, and that when they were most she was worst That before her Speech us'd to go off, she constantly lost, for an Hours space, the use of her Left Arm, that when her Speech was leaving her, she would stammer out some few Words, and after this, on a sudden, became mute And that when not able to speak, she often moaned, and made a melancholy complaining Noise, that her Speech did use to return (as it went off) all on a sudden, and at once She always had, as her Speech ceased, and two Hours after it was gone, a Pain in her Left-side, including Arm and Leg, her Left-Foot was then drawn up, as before-mention'd Her Face was high-colour'd when she lost her Speech, pale when it return'd No Part of her Body wither'd but the whole generally Cold Some time before she was at first struck Speechless her Hands used to tremble, but have been of late more steady Nor was she now so dull and heavy as formerly, but for the Generality, more brisk and chearful than in her State of Health When she has her Speech she goes best, but is always forc'd to use a Stick, being never able to go steadily She speaks by Intervals as distinctly as ever, and as loud, can sing, when capable of speaking, but at no other Time

I found, that the Mother sometimes had *Convulsive* Fits, and though a poor laboring Woman, was extremely *Hysterical* And I observ'd the Daughter to have a pale sickly Look a heavy Eye, a low Pulse, and to be

much wasted in Flesh She continu'd in my Neighbourhood about 2 Months, and I saw her almost every Day for the Whole Time I then repeated the former Course, furnishing her with large Quantities of her old Medicines, and so dismiss'd her, with Orders to let me hear again from her, when the Physick should be all spent Accordingly, in *Sept* 1688, she came (with her Mother) from *Stow* to *Oaon* (that is almost 20 Miles) on Foot I gave her a further supply of Medicines, and by the 10th of *Nov* following she was grown strong, and to all Appearance as well as ever For two Months, then last past, she did go and speak every Day, but not at all Times, of the Week, for her Speech left her (as formerly) on *Tuesdays*, but (now) return'd the next Day after Noon Thus she continu'd to the Summer following, not speaking (in more than 20 Months) on any one *Wednesday Morning*

In the *Summer*, 1689, Hoping to compleat the Cure, I procur'd for her a large stock of Medicines for the Winter following, but from that Summer, to this of 1698, I have heard nothing of her

There was some of Opinion, that this young Woman counterfeited, but upon strict Examination, I could never find any Reason for that Suspicion And I beg leave to say, I think it was not in her Power so to do

It is obvious that this is a clinical description of a patient with periodic paralysis The description does not conform in all respects to one typical of family periodic paralysis, but is surprisingly similar for one 250 years old It is atypical in so far as the patient was a female without a famulial history of periodic paralysis and that during paralysis, she was unable to speak Sporadic cases of periodic paralysis, however, have been reported in females by Bender (98) and Fischl (115), and Cousot (18) and Pastine (75) have observed loss of speech in otherwise typical cases

The term periodic paralysis (*periodische lahmung*) appears next in the literature as a title for an article in 1815 Seiler (165) used it to head a communication which described a patient with what has been interpreted by Schmidt (79) as malarial paresis A translation of pertinent parts of Seiler's report is as follows

R S, a woman 53 years old,—previously strong and healthy, presently of rather cachectic and weakened body build, was up to the last delivery which took place 9 years ago, mostly well—Since the last delivery—she complained—about dizziness, headache, lack of appetite, restless anxiety

dreams, swelling of the feet —In 1800—after a severe fright she fell unconscious to the floor After she had regained consciousness, she could hear and see everything that was going on around her, but could not make it known by any signs, that she had regained consciousness, but was forced to remain lying without motion for some time —In April 1803, she lost much blood by uterine bleeding She felt now still more weakened and was daily seized by the following attacks She quickly lost the ability to move herself voluntarily When she worked, she was suddenly interrupted in the work When she stood, she had to reach for a chair quickly or had to sit down on the floor During this she retained, however, her consciousness completely She heard and saw everything that was going on around her, but she could not speak even with the greatest effort, neither could she move any muscles The limbs retained their flexibility but they fell down as soon as they were lifted and not as in catatonia The pulse was regular during the attacks, only a little slower than usual The attacks lasted  $\frac{1}{2}$  to 1 hour, after the attacks she felt weak, otherwise well

On the 2nd of November, 1804, when she was weakened by work and had contracted a cold, she was seized again by a very severe attack —Because there were no convulsions with the attacks which the patient had daily, because the consciousness was not lost, but because she heard perfectly well during the attacks and recognized all objects, because the limbs did not get stiff,—the disease is, in my opinion, to be called a periodic paralysis, which in the form as it has appeared here, spreading over the whole body, has rarely been observed —On the 4th and 5th of November the fever was lower, the attacks of paralysis, however, returned daily in the afternoon at 3 o'clock —On the 6th of February, the patient was completely free from fever, the attacks of paralysis did not occur, all functions took place regularly, the patient complained only about very great weakness On the 7th, in the afternoon the patient was seized by paralysis after a dietary indiscretion —since the 11th there had been no paralysis and the patient felt very well She remained in this state until the 6th of December On this day she was attacked again by paralysis and severe fever —On the 7th of December, the temperature was lower, the attack of paralysis returned in the afternoon at 3 o'clock —After that she was completely free from paralysis and felt well up to the 25th of December, on which day she was seized again by paralysis after the ingestion of heavy food —On the 30th of December the patient felt well,—but she complained of considerable weakness and the periodic paralysis returned daily as before —By the use of—remedies the attacks of paralysis became milder, but she was

not entirely free from them as in November of the previous year—On the 22nd of February after a cold and a dietary indiscretion the woman fell into a light fever with stomach and chest cramps, but was completely free from periodic paralysis—and remained free from 1805 until now, 1812

Other reports of periodic paralysis without demonstrable anatomical changes which were published prior to 1853 include those of Monges 1826 (144), Bataille 1829 (97), Roots 1836 (161), West 1843 (175), Bourdin 1844 (103), Freschi 1845 (117), and Thorn 1849 (174) We have considered these to be case reports of sporadic periodic paralysis and have so listed them under references

Cavaré's paper, published first in 1853, was copied by two contemporary periodicals (108), (109), and later was revised and reprinted as an original article by von Macerio (138) in 1857 A translation of the first report (107) is as follows

The 6th of February, at seven o'clock in the morning, I was called to treat Jeanne Magnas, wife of Dispans, housewife

This woman, 24 years old, had given birth, normally, to her second child, February 3rd February 5th, about noon, without known cause and while seated before the fire, this woman was waiting for her bed to be prepared, she felt peculiar sensations in her feet, these sensations reached the legs, the calves, the trunk and the arms The tongue was affected, and became so involved that the sick woman could scarcely make herself understood She was put to bed by her husband who was helped by some neighbors, for it was impossible for her to put one foot in front of the other

There was some fever, without, nevertheless, the patient having any headache She could swallow only with the greatest difficulty the drinks which were offered to her, she saw that they moved her arms, hands, but she hadn't the slightest feeling of it There existed, in a word, a general paralysis The midwife, consulted in the matter, replied that it was without doubt milk fever which was manifesting itself She thought it advisable to take some spoonful of an anti-spasmodic medicine, as well as some glasses of an infusion of barley At 3 o'clock in the afternoon, that is, 3 hours after the beginning of the first symptoms of paralysis, the pulsations slowed, the fever receded little by little, the tongue and the extremities regained the use of their functions, the paralysis, in a word, disappeared, and all was restored

The 6th, at 3 o'clock in the morning, when I saw the patient, I saw that she was experiencing great difficulty in speaking and that she swallowed

her infusions with considerable difficulty, and I recognized a general paralysis of sensation and of movement. The lochia was not suppressed, the tongue was not coated, it was moist and rose-colored, and not the least trace of headache. The milk was of a good type and abundant. The child was strong and vigorous. The pulse rate was increased (108 beats), the hearing was normal, the patient did not complain of pain anywhere. The contractility of the bladder was never diminished, and we did not resort to the catheter in order that the patient could void.

Although there was a marked relapse, not yet seeing anything serious I prescribed 2 glasses of an infusion of valerian to be taken in the daytime, and in the interval a few spoonful of a strong anti-spasmodic, 2 broths.

The 7th, in the morning, the sick woman was perfectly well. She had spent a good night, and the paralysis of the day before had lasted only 5 hours. This medicine, she said, had eased her a great deal. (64 beats).—Same prescriptions as the day before.

The same day, at 3 o'clock in the afternoon, the patient feeling some drops of sweat moisten her forehead, appreciated the prodromata of paralysis. In fact, some moments later, the sensations showed themselves in the same order, and the paralysis took hold, as on the preceding days.

Summoned to see her, I found her mind was very clear. She had no headache. Her speech was very much impaired, the paralysis of the extremities was complete, (120 beats).—Medicine with 60 centigrams of quinine sulphate to be taken as soon as the paralysis shall have disappeared, in 3 doses, at 2 hour intervals.

The 8th, in the morning, I found the sick woman perfectly well, all of the medicine had been taken. The paralysis had lasted 6 hours,—5 broths during the day, infusion of barley for fluid.

At 3 o'clock in the evening, the paralysis appeared again and persisted for 8 hours.—New medicine with 75 centigrams of quinine sulphate, to be taken 3 times, and under the same conditions as the first.

Since the prescribing of the last dose of quinine sulphate the paralysis has not appeared again, and the patient, having continued the use of anti-spasmodics, less and less, soon became well.

I had the opportunity to see the patient again today, the 3rd of June. There has not been any relapse. The patient has resumed her routine duties, and she enjoys perfect health.

This communication appears to have been the stimulus for many other reports and in the following 8 decades an extensive bibliography on the subject of periodic paralysis appeared. In most instances, it is



not difficult to segregate the cases into those with a family history and equally typical cases which appeared sporadically. The first case of familial periodic paralysis was reported by Shakhnowitsch (83) in 1882. Three years later Westphal (176) studied a sporadic case not associated with an acute infection. Contemporary German writers, Schmidt (79) and Janota and Weber (42), attribute to Westphal the first clinical description of the dyscrasia. It is believed by the writer that such credit is misplaced.

In addition to more than 400 typical cases of periodic paralysis which have been reported and which are listed under references, there has been a small number which suggested periodic paralysis in only certain respects. Since the requirements for a diagnosis of periodic paralysis have been made arbitrarily more rigid by us in the literature published after 1853, atypical cases reported since that time are listed in the bibliography under miscellaneous. These include communications by the following, Cullen 1871 (190), Rockwell 1877 (212), Bennett 1884 (185), Suckling 1889 (217), Rich 1894 (211), Meredith 1896 (207), Donath 1900 (192), Knapp 1904 (200), Gatti 1911 (195), and Lewandowsky 1916 (203).

Comprehensive reviews of the subject of periodic paralysis during the past half century include those of Goldflam 1890 (28), Taylor 1898 (88), Schmidt 1919 (79), Janota and Weber 1925 (42), and Ribadeau Dumas 1934 (159).

#### INCIDENCE

Most observers affirm that periodic paralysis is a rare malady. The number of references given at the end of this review casts doubt upon this affirmation. In available literature there are case reports or references to more than 400 patients suffering from periodic paralysis. Besides this significant number there are several reports of periodic paralysis in publications not available in this country.

#### Sex

Contrary to the high incidence of females in the early case reports, there is a strong predilection for the male sex, Bender (98). The ratio of males to females among those with a family history of paralysis is

about 3:1 If the case reports are subdivided, one discovers that the highest incidence among women occurs in families with coincidental thyroid disease and palsy Among the sporadic cases, the ratio of males to females is much greater in fact there are few authentic instances of affected females in this group

### *Age*

Symptoms of periodic paralysis develop usually in the first or second decade of life Among one hundred and fifty-two case reports which include this information, forty had symptoms of paralysis before the age of 10 and ninety-two had symptoms before the age of 16 In addition, several complained of periods of muscle weakness months or years before the appearance of clear-cut paralysis

The onset of symptoms at a very early age has been reported by a few observers Buzzard (12) described a family in which the mother and her children had intermittent attacks of paralysis from the time they were able to make purposeful movements Schoenthal (80) described two children in their second year who were known to be afflicted as soon as they were able to walk Goldflam (32), Strauss (171), and Kulneff (49) report similar cases At the other extreme, Kramer (135) reported one patient to have had the first seizure at the age of 56, and five patients reported by Shinosaki (85) did not develop symptoms until the 4th decade of life A progressively earlier development of paralysis in succeeding generations of one family was observed by Biemond and Daniels (10) Attacks of paralysis appeared at puberty in the first generation, members of the second generation were affected at the age of 7 or 8, while in the third generation, symptoms appeared before the age of 6

Not only do symptoms usually appear at puberty or during adolescence but they are also most troublesome in this period There is a tendency for attacks to diminish in frequency and intensity during middle life and to disappear in late adult life Goldflam (28) however mentions five patients who were 50 years or older and who continued to be troubled with periodic attacks Two died at 54 and 60, respectively without having enjoyed a prolonged period of freedom from symptoms since their onset in youth

*Race*

Patients with periodic paralysis appear to be widely distributed throughout the world. Jews are affected [Mankowsky (53), Weiss (91), Atwood (6)], as well as Gentiles. Although the majority of cases have been reported from Germany, Japan, England, France, and the United States, they have been reported also from Norway, Denmark, Holland, Spain, Italy, Russia, Poland, India and Brazil. Gordon, in discussing Potts' communication (153) said that he believed that he had observed periodic paralysis in a negro.

## GENETICS OF HEREDITARY PERIODIC PARALYSIS

The first mention of the hereditary character of the affliction was by Shakhnowitsch (83) in 1882 who described a father and son with transient palsy. In 1886 the family incidence was discussed at length by Cousot (17). It is of interest to note that a commission was appointed (206) to investigate the report of Cousot, presumably because it was unique and considered to be significant. It is gratifying to record that the commission approved of his remarks and recommended that he continue his researches on the strange malady.

The fact that periodic paralysis may skip one or more generations implies that the character in such families is a recessive, Khan (46). In other families, it appears to be dominant, Saunders (215). The trait may be transmitted through either parent. A further discussion of the hereditary aspect of the malady is given under Association with Other Diseases. Comment is made in that section of the association of muscular atrophy, migraine and epilepsy in families with periodic paralysis. It has been observed that siblings who do not suffer from periodic paralysis may have one of the three above-mentioned conditions.

Charts of the genealogical tree of two families with periodic paralysis comprise Figures 1 and 2. Figure 1 is modified from Biemond and Daniels (10). Periodic paralysis and muscular atrophy are interwoven in this family. Data of the family reported by Schmidt (79) were used to construct Figure 2.

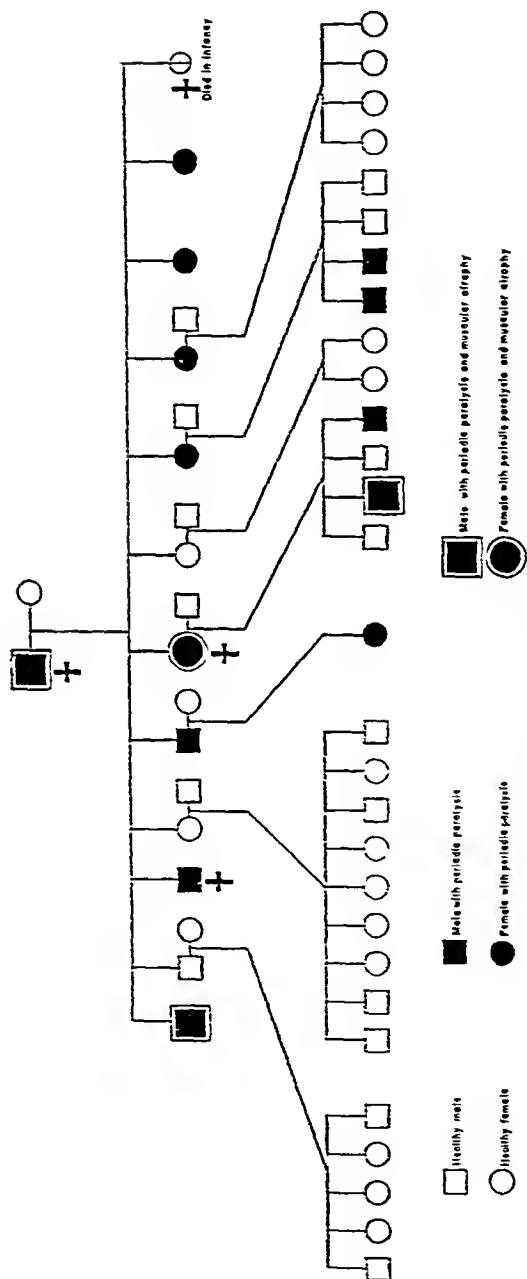


FIG. 1 GINIOTONIC TRIBE OF FAMILY Y WITH PERIODIC PARALYSIS AND MUSCULAR ATROPHY  
Constructed from data of Blomond and Daniels (10)

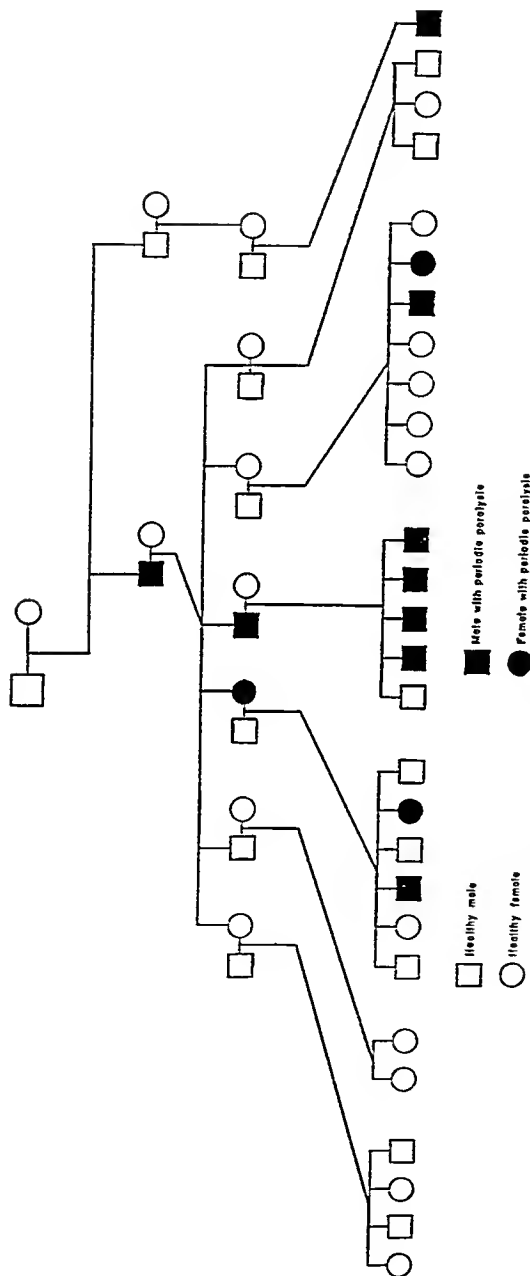


FIG. 2 GENOLOGIC TREK OF FAMILY X WITH PERIODIC PARAMETER

Constructed from data of Schmidt (79)

## CLINICAL DESCRIPTION

*Inciting factors*

There are several inciting factors of acute attacks of paralysis which have been recognized by observers and investigated intensely in many instances. Items which may be classified under the general heading of traumata constitute the majority. The trauma may be severe and debilitating such as scarlet fever [Westphal (176), Goldflam (30)], typhus fever, acute otitis media, upper respiratory infection or acute nephritis [Fischl (115)], or it may be no more hazardous than exposure to cold and dampness [MacLachlan (52)], or minor physical disability. Other episodes which have been implicated as inciting agents include, a muscle biopsy [Kastan (45)], excessive physical exertion, prolonged bed rest [Schoenthal (80), Shinosaki (84)], a menstrual period [Bender (98), Janota and Weber (42)], emotional excitement [Taylor (88)], coitus [Mankowsky (53), Longo (51)], constipation [Schoenthal (80)], and ingestion of large quantities of carbohydrates.

Many patients report that their attacks are more frequent in the winter than in summer [Kaufman (131)]. This observation has been utilized experimentally in the precipitation of acute paralytic seizures [Neel (64)]. Zabriskie and Franz (96) exposed for 35 minutes the right hand and forearm of a patient to a temperature which varied between 10° and 14°C. After 20 minutes, the relaxation of the flexors of the fingers following voluntary contraction was distinctly slowed. At 35 minutes, there was practically complete paralysis of the flexors and extensors of the fingers. Muscular irritability to mechanical stimulation was lost in the muscles of the forearm, the biceps reflex was absent, and no response to electrical stimulation could be obtained. All responses were normal on the untreated arm. The attack of local paralysis wore off slowly and 12 hours afterward, the hand and forearm were still somewhat stiff.

The ingestion of a high carbohydrate meal [Putnam (156)] is an inciting agent frequently mentioned. The regularity with which attacks develop in the middle of the night is thought to be the result of the ingestion of a high carbohydrate meal during the previous evening. Kramer (134) observed that the ingestion of 108 gm of protein, 86 gm of fat and 310 gm of carbohydrate would not lead to a paralytic attack. If, however, 133 gm of protein, 87 gm of fat

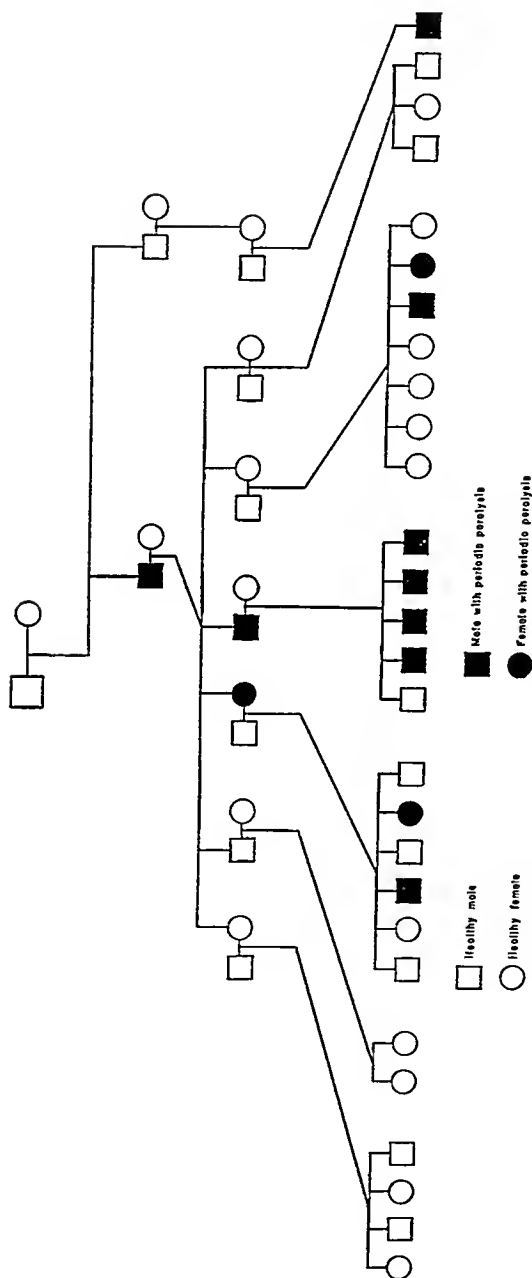


FIG 2 GENELOGIC TREE OF FAMILY WITH PERIODIC PARALYSIS

Constructed from data of Schmidt (79)

adrenalin secretion which follows parenteral administration of insulin. A period of several hours may elapse after the injection of insulin before the development of paralysis. There are no reports of the intravenous use of insulin in patients with periodic paralysis, a combination of circumstances which might hasten onset of symptoms.

Other drugs which have been employed experimentally in the precipitation of attacks, but which have not been investigated methodically, include extract of thyroid [Mitchell (60), Shinosaki (85)] physostigmine [Schoenthal (80)], atropine [Kasten (45)], pilocarpine, adrenal cortical extract [Allott and McArdle (4)], parathormone [Dunlap and Kepler (114)], pituitrin [Kasten (45)] luminal [Zabriskie and Frantz (96)] and acetylcholine [Pudenz et al (77)]. The mechanism of the action of several of these substances will be discussed under pathogenesis. Attacks produced experimentally appear to be indistinguishable from those which appear spontaneously.

### *Prodromata*

Many patients are conscious of prodromata, others may be unaware of an impending attack. Some experience a heavy, sleepy and tired feeling, others a feeling of warmth in the extremities. Irritability, nervousness [Putnam (156)], apprehension [Sugár (173)] indigestion, constipation, diarrhea [Crafts (111)], headache, fever [Byrne (13)], weariness, aching in the legs [Gardner (119)] fatigue, sweating, numbness [Hartwig (126)], somnolence, tachycardia [Goldflam (28)] bilateral ptosis [Gillespie (123)], strangura [Westphal (176)] and thirst [Taylor (88)], have been mentioned. This seems to be no more than a list of symptoms which any man may fall heir to. None of them are particularly specific for periodic paralysis. In some patients they may appear as long as 24 hours in advance of an attack. Other patients feel exceptionally well on days preceding symptoms and awaken during the night or early in the morning with frank paralysis. The development of symptoms is not painful and many patients sleep soundly during the incipient stages. At other times, they awaken in the early hours of the morning with a sensation of stiffness or weakness of the extremities. Further sleep is followed by fully developed palsy. More rarely, attacks begin during the day in the pursuit of routine duties.



and 470 gm of carbohydrate were substituted, an attack ensued. This observation was amply confirmed by Shinosaki (85). Paralytic attacks occurred in eight susceptible patients from 4 to 9 hours after the ingestion of more than 600 gm of rice, from 200 to 300 gm of cane sugar achieved a similar effect. If a high protein diet were taken instead (600 to 800 gm of meat), no attacks followed. He believed that patients afflicted with periodic paralysis have a decreased tolerance to glucose. Aitken and associates (2), however, could not confirm this and observed a normal tolerance to glucose during an attack as well as in the interval period. In the patient studied by us we were successful in inducing an attack on 4 occasions following the ingestion of 100 gm of glucose. This patient appeared to develop a tolerance to the experimental procedure, however, and when it was repeated on successive days weakness only, without frank paralysis, developed. Shinosaki (84) believed that a prolonged hyperglycemia rather than one of short duration was necessary to induce symptoms. He cited experiments in which a hyperglycemia of less than 1 hours duration, which followed the intravenous injection of from 18 to 30 gm of glucose, did not produce paralysis in susceptible persons.

Precipitation of attacks by epinephrine or adrenalin [Orzechowski (150), Pelz (152)], is associated presumably with their blood sugar raising and serum potassium lowering properties. Neither drug appears to be as consistent in inducing paralysis as is a high carbohydrate meal [Favill and Rennick (23)]. Shinosaki (85) was successful only 3 times in 12 in producing symptoms with the injection of from 0.005 to 0.001 gm of adrenalin. The persistence of the post-adrenalin hyperglycemia for at least 3 hours was necessary to produce paralysis. Pudenz and associates (77) obtained more consistent results with epinephrine given subcutaneously or orally as the sulphate (0.1 gm). Allott and McArdle (4) observed that patients in whom attacks could be induced repeatedly by injections of adrenalin were those in whom emotional factors were equally effective in bringing on symptoms. Conversely, adrenalin-resistant patients exhibited little correlation between paralytic episodes and emotional traumata.

It is noteworthy that insulin alone or insulin combined with glucose is as effective an inciting agent as is prolonged hyperglycemia (4), (77). It seems reasonable to attribute the effect to stimulation of

pectorate may be noted in those mildly affected. Ptosis and blurring of vision from weakness of the extraocular muscles have been observed by Singer and Goodbody (166). Involvement of the motor branches of the trigeminal nerve has been reported by Taylor (88).

Neither impairment of consciousness nor impairment of mental faculties, accompany paralytic attacks. It is mentioned frequently in the literature that patients who have died during an attack have maintained clarity of thought until the end. The superior mental capacity of one family affected with periodic paralysis has been stressed by Taylor (88).

A transient anuria [Wexburg (92)] is a rather frequent complaint. This has been assumed to be caused by a diminution in desire to void rather than spasm of the sphincter or inability to void due to obstruction along the course of the urethra. From the observations made on the patient studied by us it was concluded that during paralysis less urine was passed from the bladder because less urine was secreted by the kidneys. A diminution in intake of fluids is an important factor in this chain of events. Erection of the penis during an attack has been reported. Spontaneous movement of the bowels during paralysis is uncommon. Few symptoms other than those mentioned already accompany paralytic seizures. Anorexia, nausea, vomiting [Gardner (119)], cramps in affected muscles [Hartwig (125)], sweating, congestion of the conjunctivae and bronchial mucosa, coughing [Vogt (90)], and mild paresthesia [Buzzard (12)] have been described.

Physical measurements of the extremities during paralysis may reveal an increase in the circumference of arms and legs [Wexberg (92), Šerko (82), Kastan (45)]. In one patient studied by Neel (63), the circumference of the thigh was 8 cm greater during paralysis than it was after. Similarly, the circumference of the forearms increased more than 2 cm during the height of the symptoms.

The sensory examination usually is negative. In most patients, there is no loss of temperature, touch, pain or vibratory sensibility. Fischl (115) alone has reported loss of sensibility in one patient during an attack. The deep and superficial reflexes are abolished in severely paralyzed areas. These include biceps, triceps, knee jerks, ankle jerks, and plantars. Cremasteric, abdominal and epigastric reflexes are retained usually. Affected muscles are not painful, but muscle soreness may be elicited on careful manipulation.

*Paralysis*

Paralysis begins peripherally in the legs and progresses centrally. Legs, arms, trunk and neck may be the order of involvement. In a few patients, the paresis begins in the muscles of the hips and shoulders and spreads to the periphery. Paralysis may be partial or complete, localized or generalized, either the upper extremities or the lower extremities alone may be involved, or it may be unilateral [Burr (106)], with little or no paralysis of the other half of the body. The paralysis is apt to be most profound in the leg muscles.

In a fully developed attack the patient lies helpless in bed, unable to raise the hands, move the limbs or change position. If an extremity is elevated, it falls lifeless on to the bed. If unsupported, the head drops on the sternum or backward between the scapulae. The impression is gained of "a patient with a broken neck lying in bed, motionless, able to speak and think clearly, but utterly unable to defend himself beyond indicating his wants and giving directions to have his head or extremities shifted" [Holtzapple (41)]. The extensor muscles are more seriously affected than the flexors. The paralysis is a flaccid motor type which may involve all of the voluntary muscles except those of the face, mouth, throat, accessory muscles of respiration and the sphincters of the rectum and bladder.

Many minor episodes which occur by day or escape unnoticed at night are of an abortive type ["crises frustes," Hirsh (37)], ["attaques abortives," Oddo Audibert (69)]. They have been described vividly by Holtzapple (40) as "feeling the spell" and vary from stiffness and weakness in the extremities to mild paralysis with weakened responses of the deep reflexes [Maclachlan (52)]. In some patients there may be incoordination of the finer movements for as long as one week without development of paralysis.

Involvement of the muscles of respiration as well as those which participate in deglutition and phonation is unusual but when this occurs the consequence is serious. Maclachlan (52) has reported a fatal ending of such an involvement in one patient. Impaired phonation is caused presumably by a combination of paresis of the muscles of respiration and paresis of the muscles of the neck which are inserted in the larynx and pharynx [Goldflam (28), Taylor (88), Mitchell (58)]. Inability to breathe deeply [Hirsch (37)], cough, sneeze or ex-

frequent attacks over a period of years that the arm jerks were sluggish and that 'there was a permanent loss of knee-jerks and ankle-jerks' Taylor (88) noted a failure of reaction of the peroneal group of muscles between attacks and Goldflam (29) obtained a partial Reaction of Degeneration with weak currents. These variations are caused presumably by secondary changes in muscles which have been subjected to repeated and prolonged periods of paralysis.

An increase in the chronaxie of affected muscles during paralysis has been observed by de Bruin (104) and Ribadeau Dumas (159). Between attacks the chronaxie is normal [Strauss (171)]. A positive Chvostek's sign has been noted in patients in attack-free periods [Wexberg (92) Janota and Weber (42)]. The significance of this is not appreciated by the writer. One explanation is that muscle irritability and not nerve irritability is responsible for an apparent Chvostek.

There appears to be a significant distinction between periodic paralysis and curare poisoning in regard to electrical excitation. Following curare poisoning the muscle responds normally to direct stimulation and the nerve only is unresponsive.

The internal organs of the body which show evidence of disturbance in association with periodic paralysis include the heart and blood vessels and the endocrine glands notably the thyroid. A bradycardia frequently appears during attacks [Oddo (69) Schlesinger (164), Pastine (75)], in others an arrhythmia or a hypotension may develop. More than a score of observers have detected during paralysis a transient dilatation of the heart whether by percussion [Westphal (177) Noone (67)] or by fluoroscopy [Fuchs (118)]. The dilatation has been attributed by Mitchell (57) to a relaxation of the cardiac musculature. Accompanying the dilatation of the heart, there may be heard a systolic murmur either at the apex or base, accentuation of the second pulmonic sound or a weakened quality to all of the sounds. No cardiac abnormalities persist after recovery from paralysis. Enlargement of the thyroid, with or without signs of thyrotoxicosis may be observed.

### *Recovery*

Recovery proceeds anatomically in the reverse order to that in which paralysis develops. Return of function begins usually in the

A disturbance of the electrical reactions of affected muscles usually accompanies severe symptoms. The characteristic changes are a loss of direct and indirect electrical excitability. The loss varies from complete unresponsiveness to a minimal diminution only. The more profound the paralysis, the greater the loss of irritability. During recovery and in the interval periods, both muscles and nerves respond normally. Hartwig (125) was the first to investigate this phenomenon in a patient with periodic paralysis. His communication appeared only 6 years after Erb's original description of the procedure. He was so impressed with the failure to obtain an electrical response during an attack of paralysis that he believed his apparatus was at fault.

The subject of electrical excitability in patients with periodic paralysis was investigated thoroughly by Mitchell (57) in 1899. It seems best to quote directly from his communication:

In one examination during an attack it was impossible to get any reaction either with faradic or galvanic currents in most of the muscles with the largest amounts of current bearable. During another profound attack, in which it required from 20 to 30 milliamperes, C C C being greater than A C C, to develop contraction by the usual method, when a large electrode was placed upon the sacral region and a gold needle inserted deep into the body of a muscle, it was found that fair contracture could be induced with 8 milliamperes, C C C greater than A C C, interrupting current at the needle insertion into the muscle. On repeating this experiment upon a healthy person it was found that less than half this amount of current was required to evoke contraction in the muscles. There was never at any time any suggestion of reversal of the poles, C C C was always greater than A C C in the examinations. Nerves show the same lowered irritability. If it requires from 20 to 30 milliamperes to induce contractions in a group of muscles no less is required to bring about contraction when the nerve is stimulated. Strong currents applied either to the nerve or muscle do not cause the usual amount of discomfort.

It has been noticed, also, that during paresis the skin resistance is increased [Oppenheim (149)]. This is not altered by immersion in water.

While the above findings are applicable to the majority of afflicted persons, a few patients have been observed who have not shown a normal response to mechanical or electrical stimulation in attack-free periods. Maclachlan (52) observed in one patient who suffered from

of carbohydrate metabolism is thought to be responsible for the other disturbances. This factor will be discussed under pathogenesis.

### *Spinal fluid*

No change in dynamics or cell count has been reported [Wexberg (92), Vogt (90), Bender (98)]. A slight increase in total protein may accompany a severe attack [Ribadeau Dumas (159)]. Zabriskie and Frantz (96) found a total protein of 22 mgm per 100 cc in an interval period and 28 mgm per 100 cc immediately following paralysis. In the patient reported in this communication the protein was 20 mgm per 100 cc 24 hours following an induced attack of paralysis.

### *Metabolic rate*

An elevation of the basal metabolic rate is anticipated in patients with combined thyrotoxicosis and periodic paralysis although few observations of this function are reported. In patients without thyrotoxicosis an increase in rate during paralysis has been noted by several investigators [Edsall and Means (22), Zabriskie and Frantz (96) and Kirk and Moller (133)]. The greatest increase was observed by Kirk and Moller who reported a change from +17 to +59 per cent during development of paralysis. Such observations seem paradoxical. With decreased motor activity of the skeletal musculature one might predict a decrease in oxygen consumption. It is unlikely that the increased oxygen consumption follows in the wake of an immediate increased need for energy requirements. A more acceptable explanation to us is that a transient disturbance of the intermediary metabolism of carbohydrates demands an increased oxygen intake.

### *Electrocardiography*

The electrocardiogram during paralysis shows striking and unusual changes from the normal. In 1912 Atwood (5) noted right axis deviation in a patient aged 7. Janota and Weber (42) discuss at considerable length small abnormalities in 2 patients. These changes and others have been studied extensively by Zabriskie and Frantz (96) who noted a decreased amplitude of the T waves and by Stewart and associates (86) who observed a bizarre form of the electrocardiogram. These observers noted a prolongation of the P-R, QRS and Q-T

neck and upper extremities and appears last in the lower extremities. The length of time for recovery may be as long as the period of development of symptoms. A residual soreness and stiffness of the affected muscles may persist for one or two days. During recovery an increased urinary output has been observed. The patients are otherwise essentially normal persons.

### *Frequency and duration of attacks*

There are no recognized predictable criteria regarding frequency. Patients may have only one or two attacks in a lifetime, others have two or three a decade, others two or three a year, yet others, several each week. The patient reported by Zabriskie and Frantz (96) suffered one attack each night for 10 years following his thirteenth birthday. A cyclic occurrence has been noted by several investigators [Mitchell, Flexner and Edsall (59), Gardner (119)], attacks even may occur on certain days of each week [Musgrave (148), Putnam (156)].

Attacks vary tremendously in duration. Abortive attacks may be very transient and not incapacitating. An average duration is probably 6 or 8 hours. Some attacks have lasted 3 or 4 days [Diller and Rosenbloom (21)]. The longest authentic period of paralysis with recovery is 8 days [Machlachlan (52)].

## LABORATORY STUDIES

### *Formed elements of the blood*

No change in red blood cell count during paralysis has been reported. The white blood cells may show an absolute increase in number with a relative lymphocytosis [Taylor (88)].

### *Serology*

The complement fixation reactions for syphilis when reported have been negative.

### *Urine*

A transitory albuminuria [Infeld (128), Yoshimura (95)], cylinduria [Schlesinger (164)], acetonuria and glycosuria [Shinosaki (84)], have been observed during attacks. The first two disturbances are presumably associated with a diminished urine output. A disturbance

TABLE I

Experimental observations on blood

DATE	TIME	WHOLE BLOOD		SERUM										CELLS				REMARKS	
		Cell volume per cent	Sugar mg per 100 cc	Total fixed base m eq per liter	Sodium m eq per liter	Potassium m eq per liter	Calcium m eq per liter	Total CO <sub>2</sub> m eq per liter	Chloride m M per liter	Phosphate m eq per liter	Protein gm per 100 cc	Non-protein nitrogen mg per 100 cc	pH	Total fixed base m eq per liter	Potassium m eq per liter	Water m eq per liter	Total phos m eq per liter		
Average range for 1000 mals																			
1938																			
March 27	8 30 a m	40.44	80	120	150	155	139-141	3.5-4.5	4.7-5.4	25-27	102-106	1.0-1.5	6.4-7.5	20-35	7.40	108.5	85.8	25.2	9 17 a m 100 gm glucose p o
March 27	1 45 p m	41.5	126		152.7	140.7	2.6	4.6	21.1	101.9	0.6	7.1	23						1 03 p m beginning of paralysis
March 30	5 35 p m		140		151.3	143.5	2.6	4.3	25.9	103.7	1.4	6.5							7 00 p m complete return of motor function
April 7	8 15 a m	41.5	236		150.5	141.4	2.3	4.2	26.0	103.8	0.8	6.5			109.1	83.0	691		6 00 a m 100 gm glucose p o
April 7	11 45 a m	40.4	152		151.2	141.3	2.6	4.4	26.6	103.7	1.0	6.6			111.1	82.9	712	20.7	8 00 a m beginning of paralysis
April 7	6 15 p m	38.6	121		153.6	141.9	3.4	4.6		101.5	1.5	6.5			111.6	85.1	705	23.1	5 00 p m complete return of motor function
April 13	10 30 a m	39.4	88		152.5		3.4	4.5	21.3	103.2	2.1	6.7			108.5	78.6	711	24.3	20 gm KHSO <sub>4</sub> during previous 24 hours
																			100 gm glu cose p o No paralysis
April 13	1 05 p m	38.4	122		153.2		3.8	4.3	25.4	103.5	1.9	6.8			110.6	82.5	709	25.9	No paralysis
April 18	9 00 a m	40.0	94		153.9		3.0			98.9	1.4	6.8			109.6	77.9	717	24.3	15.8 gm K <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> during previous 24 hours
																			glucose p o No paralysis
April 18	10 00 a m	39.1	218		149.3		2.8			100.3	1.1	6.6			109.6	80.4	723	22.6	No paralysis
April 22	9 00 a m	38.7			153.2		3.3	4.4		102.7	1.8				109.1	83.8			19.6 gm (NH <sub>4</sub> ) <sub>2</sub> HP0 <sub>4</sub> during previous 24 hours
																			glucose p o No paralysis
April 22	1 15 p m	37.5			154.4		3.6	4.3		103.7	2.0				105.9	80.0			No paralysis
April 24	9 15 a m						3.4												6 00 a m 100 gm glucose p o Paralysis
April 27	8 40 a m				150.6		2.4				0.7	6.9			106.3	77.1			6 00 a m 100 gm glucose p o No paralysis
April 27	10 40 a m				152.6		2.5				0.9	6.6							Paralysis
May 8	7 40 a m				152.9		3.5												No paralysis
May 8	8 40 a m				153.1		3.9												No paralysis
May 8	10 50 a m				155.5		4.1												No paralysis
May 14	8 26 a m				152.2		2.8					6.8							6 00 a m 100 gm glucose p o No paralysis
May 14	9 26 a m				150.0		2.9					6.5							No paralysis
May 14	11 26 a m				151.9		3.0					6.7							No paralysis



intervals, alteration in the form of the R-T segments as well as a decrease in amplitude of the T waves. All of the variations were observed with a decrease in concentration of serum potassium.

### *X-ray*

An increase in the size of the heart [Poulsen (154), Wexberg (92)] is the only disturbance during paralysis to be detected by x-ray examination that has been reported in the literature.

### *Chemical constituents of the blood*

The various chemical constituents of the blood of the patient whose history is included in this review are given in Table I. Several bloods were collected before or after an attack of paralysis, the others were collected during paralysis. There are two constituents whose concentrations are altered during paralysis that are believed to be particularly significant. These are serum potassium and serum phosphate. Both show a decrease in concentration during symptoms and a normal level in the interim. These changes are believed to be intimately concerned with the pathogenesis of paralytic attacks. Appreciation of their significance marks an important step in the understanding of neuro-muscular physiology as well as in the understanding of periodic paralysis.

Biernard and Daniels (10) were the first to report a diminution in concentration of serum potassium during a spontaneous attack. They observed a value of 3.8 milliequivalents per liter in comparison to an interim level of 4.7. It is unlikely that they appreciated the significance of this finding since they did not comment upon it. Nor was it appreciated by others until the following year, when Walker (222) reported a 50 per cent decrease in concentration of serum potassium during an attack of paralysis. Such a change in the concentration of an acid or base constituent of the serum indicates a profound disturbance of electrolyte equilibrium in the body. Since 1935, Ferrebee, Atchley and Loeb (25), Pudenz et al (77), and Gammon et al (27) have published ample data to substantiate the original observations.

A diminution in serum potassium is thought to be a relatively constant finding during attacks of periodic paralysis, whether heredi-

during paralysis in susceptible persons as they do in normal persons, as Harrop and Benedict have shown (197) following parenteral administration of insulin. Other data which suggest a disturbance of phosphate metabolism in periodic paralysis are those of Brand and Harris (187). In the study of a biopsied specimen of muscle from an afflicted person they observed a diminished content of creatine and acid-soluble phosphate.

The concentration of the other constituents of the blood shows no uniform deviation from the normal. Yoshimura (95) observed an increased concentration of blood magnesium during paralysis with a relative decrease in the calcium-magnesium ratio. The significance of this finding is not obvious to us although it was attributed by him to a disturbance of carbohydrate metabolism. In our patient there was a tendency for the concentration of total base, sodium and calcium to decrease during symptoms. Total bicarbonate, chloride and protein showed little change. The pH of the serum, determined during the attack, was normal. Studies of total fixed base, potassium and phosphate of the blood cells contributed little.

The concentration of blood sugar has been studied by many observers. Some report a concentration above normal during paralytic attacks, others report a hyperglycemia in patients with a coexisting thyroid dyscrasia, while others have observed a hyperglycemia in attack-free periods. It is concluded that the level of sugar in the circulating blood bears no constant relation to paralytic attacks. Edsall and Means (22) observed a normal concentration of lactic acid during symptoms while Tsuji (89) noted a significant increase in this constituent above the preparalytic level.

The concentration of serum non-protein nitrogen was normal during one attack in our patient and has been so reported in other patients. Further study of this constituent might reveal a transient increase during attacks which are accompanied by oliguria.

#### VOLUME OF BODY FLUIDS

Plasma volume, blood volume and interstitial fluid volume were determined in our patient under various conditions (Table II). Before the first experiment 100 gm of glucose was given orally in the expectation that an attack of paralysis would be precipitated. This

tary or sporadic in type or following excessive assimilation of desoxycorticosterone acetate. The diminution follows closely the development of symptoms. In some attacks a quantitative correlation has been observed between severity of paralysis and decrease of serum potassium. Aitken et al (2) noted that muscular weakness developed when potassium reached 3.0 milliequivalents per liter and paralysis of the extremities was complete when potassium was 2.5. Values as low as 1.2 milliequivalents per liter have been observed by Allott and McArdle (4) during severe attacks. In our patient, the lowest level observed during symptoms was 2.3 milliequivalents per liter. During the 4 episodes which were investigated systematically by us, the serum potassium varied from 2.3 to 3.4 milliequivalents per liter. A return to normal as paralysis subsided was a constant observation.

Probably as important as the absolute level in the production of symptoms is a relative decrease in concentration. Thus, a decrease from 4.5 to 3.0 milliequivalents per liter may be as important for the institution of paralysis as is a similar decrease from 4.0 to 2.5 milliequivalents per liter. This is illustrated in an experiment by Gammon, et al (27). Before injection of adrenalin in a susceptible person, the concentration of serum potassium was 5.4; 45 minutes later paralysis had developed and the concentration was 3.7. During recovery the concentration returned to 4.2, a level somewhat below that observed before the onset of paralysis.

In any syndrome with which is associated a transient alteration of the concentration of one acid or base constituent, it is not unreasonable to anticipate a concomitant change in concentration of one or more other constituents. During attacks of periodic paralysis, a diminution in concentration of serum phosphate (4) accompanies the diminution in serum potassium. The altered concentration of the first constituent has received scant attention in the zeal to investigate the dysfunction of potassium metabolism. It may be that the change in phosphate concentration possesses less pathological significance than does that of potassium or it may be intimately related to a disturbance of hexos-phosphate metabolism in the muscle as postulated by Allott and McArdle (4). Whichever may be the correct explanation, potassium and phosphate appear to leave the serum

procedure on the first day of the period; on the second and third day, weakness only developed. The negative calcium and phosphate balance in periods No. 1 to 5 is believed to be related to a change from active to sedentary habits. Milhorat and Toscani (55) observed a negative phosphate balance in a patient with periodic paralysis, but no disturbance of calcium exchange. They attributed the dissipation of phosphate to a disturbance of muscle metabolism. The balance data of the other constituents for the 4 day periods (Table IV) suggest that equilibrium of each was maintained.

In contrast to the 4 day periods, the daily analyses of urinary constituents showed significant variations. During each of the 3 days in which attacks were induced there was a diminished excretion of sodium, potassium, total fixed base and chloride. The diminished excretion of potassium on attack days confirms the studies of Allott and McArdle (4) and Gammon et al. (27). The variations in the excretion of other urinary constituents were not remarkable.

#### PATHOGENESIS OF DECREASE IN SERUM POTASSIUM

The pathogenesis of the decrease in concentration of serum potassium during paralysis is not defined with certainty. There are 2 likely paths of exit from the serum; (1) into bladder urine with subsequent excretion; and (2) into blood cells or tissue cells without loss from the body. Studies of urinary potassium before, during, and after an attack of paralysis show no spontaneous diuresis during symptoms. In fact, the observations of Gammon et al. (27) as well as those presented in Table III show a diminished excretion of potassium during paralysis. It appears unlikely, therefore, that a loss of potassium from the serum is caused by a loss of potassium from the body.

The second hypothesis is more difficult to investigate. An increase in concentration of potassium in red blood cells during paralysis has been observed neither by Pucenz et al. (77) nor by us (Table IV). To sample the tissue cells in man in order to determine whether or not a gain in content of potassium has occurred offers certain technical difficulties. A mass migration of potassium might be investigated indirectly from the study of body fluid volumes if the technique for the determination of these values were more precise, but such is not a

was accomplished and the several fluid volume measurements were obtained during deep paralysis. The patient was fasting before the second experiment and had been free from paralysis during the preceding 3 days. The third experiment was performed as a control for the previous ones. It was preceded by the ingestion of 100 gm of glucose but no paralysis ensued. The data from the three experiments are similar. In each there was observed a volume of plasma, blood and interstitial fluid greater than normal. It is believed that these changes may be significant, whatever may be their interpretation they should be confirmed. They will be discussed under pathogenesis.

TABLE II  
*Body fluid volume studies*

DATE 1938	PLASMA VOLUME		BLOOD VOLUME	INTERSTITIAL FLUID VOLUME		REMARKS
	cc	cc per kg	cc	kg	per cent body weight	
April 27	1730	57	2820	9.8	33	100 gm glucose before test Paralysis during test
May 8	1720	57	2680	9.7	33	No preliminary treatment No paralysis
May 14	1770	59	2750	9.2	31	100 gm glucose before test No paralysis

#### INTAKE AND OUTPUT OF CHEMICAL CONSTITUENTS

The balance data obtained from the metabolic studies on our patient are given in Tables III and IV. A description of the technique for the collection of the metabolic data is given in the case report. The study was divided into 4 day periods. During each period a constant diet was consumed and all urines and stools were collected. Balance observations were made on the following constituents, sodium, potassium, calcium, chloride, phosphate, and nitrogen. In addition, the daily urinary excretion of creatine, creatinine, ammonia, total fixed base, titratable acid and the urinary pH were determined.

There was no significant gain or loss of body weight, as determined daily, in association with attacks of paralysis. Nitrogen balance was achieved in all periods except No. 8. In this period, the patient was given 100 gm of glucose daily. Paralysis followed this experimental

Date	VII	2000	30 0	1450	6 1	30 2	137 4	75 2	41 4	10 8	20 0	69 0	31 8	9 8	0 71	0 18	11 minima adrenalin chloride 1 1000 i v No paralysis
April 20-21		2000	30 1	1730	5 2	40 2	151 4	88 0	43 4	7 2	63 2	72 2	60 1	10 7	0 67	0 40	9 8 gm (NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub> p o
April 21-22		2000	29 9	1600	4 9	41 6	160 4	76 2	46 6	7 0	77 6	73 2	69 2	11 7	0 67	0 40	9 8 gm (NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub> 100 gm p/luce p o No paralysis
April 22-23		2000	30 0	2210	5 3	48 9	191 2	78 1	53 4	13 7	47 9	112 8	41 6	13 8	0 93	0 93	
April 23-24		2000	30 0														
April 21-25	VIII	2000	30 0	770	6 1	23 4	69 6	30 7	25 9	7 1	12 2	12 1	12 9	1 8	0 31	0 70	100 gm glucose p o Paralysis
April 25-26		2000	30 1	1450	6 2	33 2	145 5	61 0	51 8	9 1	16 6	68 4	28 8	8 8	0 67	0 31	100 gm glucose p o Weakness, no paralysis
April 26-27		2000	30 2	1550	6 6	30 4	153 6	80 4	56 2	8 0	12 0	82 8	32 0	9 2	0 69	0 38	100 gm p/luce, p o Weakness, no paralysis
April 27-28		2000	30 2	1290	6 4	25 3	135 3	71 4	50 7	7 7	17 4	71 2	30 7	8 6	0 65	0 28	100 gm p/luce, p o No paralysis
April 28-29	IX	2000	30 2	740	5 9	21 3	102 5	85 9	37 8	6 1	17 4	61 6	17 8	6 9	0 51	0 23	
April 29-30		2000	30 1	1725	6 5	26 8	151 6	85 0	59 2	6 9	21 2	84 2	10 1	9 5	0 64	0 35	
April 30 May 1		2000	30 0	1615	6 3	27 9	113 7	71 0	59 1	7 3	22 4	78 0	31 4	10 0	0 63	0 36	
May 1-2		2000	30 0	1655	6 4	25 3	156 5	91 6	52 0	7 6	17 6	86 2	34 7	9 6	0 65	0 36	
May 2-3	X	2000	29 9	1110	6 2	30 2	124 2	76 0	49 6	8 1	18 2	75 2	30 0	9 5	0 70	0 41	30 mg thiamin chloride i v
May 3-4		2000	29 9	1480	6 1	31 0	135 8	69 1	50 9	8 4	22 2	80 0	25 8	9 2	0 67	0 37	30 mg thiamin chloride i v
May 4-5		2000	29 8	1475	6 0	31 4	119 6	59 2	45 7	8 2	21 8	69 8	23 9	8 9	0 67	0 36	100 gm p/luce p o No paralysis
May 5-6		2000	30 2	1680	6 3	31 4	134 0	75 7	45 5	9 3	8 4	82 8	27 1	8 7	0 59	0 35	
May 6-7	XI	2000	30 1	1630	6 3	29 8	150 0	80 4	56 4	14 7	7 5	87 6	28 3	9 2	0 65	0 11	
May 7-8		2000	30 0	1320	6 4	27 2	157 2	101 5	49 4	12 3	7 4	96 1	29 1	10 0	0 71	0 42	
May 8-9		2000	30 0	1580	6 0	33 2	114 0	54 7	48 4	7 6	10 1	68 2	25 8	8 8	0 61	0 41	
May 9-10		2000	29 9	1330	5 9	33 6	114 0	51 7	44 0	8 8	11 3	58 8	25 2	9 7	0 61	0 51	
May 10-11	XII	2000	30 1	1860	6 1	36 2	146 0	79 7	63 2	7 8	8 1	84 2	36 5	9 9	0 65	0 32	
May 11-12		2000	30 0	1790	6 4	29 3	153 8	84 2	61 3	8 5	7 7	86 8	32 6	10 1	0 61	0 29	
May 12-13		2000	29 9	1810	6 4	29 6	156 1	90 2	59 8	8 7	8 8	89 6	33 1	9 6	0 61	0 39	
May 13-14		2000	29 9	1440	6 1	30 3	125 4	62 5	55 7	6 7	10 8	68 1	27 5	9 1	0 63	0 41	

TABLE III

Fluid intake and urine data

DATE 1938	PERIOD	FLUID INTAKE cc	BODY WEIGHT kg	URINE										REMARKS		
				Volume cc	pH	Ammonia m eq	Total fixed base m eq	Sodium m eq	Potassium m eq	Calcium m eq	Titratable acid m eq	Chloride m eq	Phosphate m eq		Total nitrogen mg	Creatinine mg
March 27-28 March 28-29 March 29-30 March 30-31	I	1500	29.6	1290	6.5	29.9	152.4	82.8	55.8	10.7	11.8	71.0	36.1	9.2	0.75	0.21
		1500	29.8	1230	6.3	21.6	145.8	68.8	51.1	12.1	20.4	75.2	32.4	10.1	0.78	0.22
		1500	29.8	1120	6.3	27.7	148.0	70.9	59.3	11.7	16.2	73.6	32.9	9.9	0.73	0.21
		1500	29.8	1130	5.7	36.8	100.4	47.4	43.0	13.4	21.0	62.8	23.5	9.3	0.75	0.17
March 31-April 1 April 1-2 April 2-3 April 3-4	II	1500	29.8	1060	6.7	26.3	162.3	81.6	49.8	9.9	12.6	87.0	31.3	9.5	0.61	0.11
		1500	29.9	1110	6.3	26.2	147.0	69.7	60.0	11.7	18.4	78.0	33.2	9.3	0.65	0.17
		1500	29.8	1260	6.3	27.1	160.9	88.8	50.6	12.0	19.0	86.2	35.9	9.9	0.68	0.33
		1500	29.8	1190	6.2	27.5	145.3	79.8	13.0	12.1	21.1	71.6	33.7	10.0	0.68	0.33
April 4-5 April 5-6 April 6-7 April 7-8	III	1500	29.8	820	5.5	35.0	105.6	42.6	46.0	10.7	27.6	58.8	28.3	9.7	0.68	0.27
		1500	29.7	1130	5.6	33.5	152.5	74.4	41.7	13.9	28.0	82.8	27.2	9.8	0.70	0.19
		1500	29.7	1170	6.6	27.1	163.7	92.8	57.5	11.2	15.2	91.0	36.9	9.4	0.67	0.26
		1500	29.7	710	6.3	33.2	105.2	53.6	36.1	13.7	17.4	58.8	27.6	9.4	0.68	0.26
April 8-9 April 9-10 April 10-11 April 11-12	IV	1500	29.9	810	6.2	26.8	117.6	44.4	55.8	11.3	17.2	62.8	29.1	8.4	0.61	0.18
		1500	29.9	1110	6.4	25.2	146.8	73.0	46.3	11.4	16.4	76.0	36.8	9.3	0.69	0.35
		1500	29.9	1250	6.5	22.8	169.8	97.2	60.0	11.1	15.8	94.4	38.9	9.5	0.67	0.31
		1500	29.7	870	5.7	27.7	122.9	57.2	49.0	10.7	25.2	64.1	28.7	9.8	0.69	0.11
April 12-13 April 13-14 April 14-15 April 15-16	V	1500	29.9	800	5.8	31.1	159.1	61.0	85.6	7.5	51.4	68.4	65.6	9.3	0.69	0.32
		1500	29.8	910	6.0	27.4	185.6	57.0	115.3	4.1	61.2	65.0	78.2	8.1	0.62	0.35
		1500	30.0	890	5.5	31.2	133.0	58.8	57.5	7.9	31.0	67.0	35.8	9.7	0.71	0.36
		1500	29.9	1220	6.1	33.4	197.4	107.4	67.5	10.4	23.2	125.0	31.1	11.5	0.88	0.34
April 16-17 April 17-18 April 18-19 April 19-20	VI	2000	30.1	1550	5.6	32.6	131.6	70.0	40.6	10.7	23.0	80.0	26.5	9.5	0.69	0.35
		2000	30.2	1830	7.1	17.4	258.1	99.0	113.1	10.7		109.0	41.7	9.2	0.64	0.33
		2000	29.9	1530	7.1	20.0	190.9	62.5	101.4	9.5		71.2	39.6	9.1	0.69	0.39
		2000	30.0	860	6.2	28.0	109.4	50.8	49.0	8.2	16.8	44.4	26.4	8.4	0.65	0.43

TABLE IV—*Concluded*

DATE 1938	PERIOD	CONSTITUENT	DIETARY INTAKE	EXTRA DIETARY INTAKE	URINARY OUTPUT	FECAL OUTPUT	DAILY BALANCE	REMARKS
April 24-28	VIII	Sodium, m eq	183	137	24	9	+16 7	April 24, 100 gm glucose
		Potassium, m eq	269		185	30	+13 5	p o Paralysis
		Calcium, m eq	173		32	139	+0 5	April 25, 100 gm glucose
		Chloride, m eq	191	137	265	5	+14 5	p o Weakness, no pa-
		Phosphate, m eq	150		104	31	+3 7	ralysis
		Nitrogen, gm	+6 4		31 4	1 0	+3 8	April 26, 100 gm glucose,
April 28- May 2	IX	Sodium, m eq	181	137	337	8	-4 2	p o Weakness, no pa-
		Potassium, m eq	262		208	29	+6 2	ralysis
		Calcium, m eq	184		28	131	+6 2	April 27, 100 gm glucose
		Chloride, m eq	191	137	310	5	+3 5	p o No paralysis
		Phosphate, m eq	148		127	38	-4 1	
		Nitrogen, gm	+4 6		36 0	1 3	+1 8	
May 2-6	X	Sodium, m eq	183	137	280	8	+20 0	May 2, 30 mg thiamin
		Potassium, m eq	267		192	30	+11 2	chloride i v
		Calcium, m eq	180		34	165	-4 7	May 3, 30 mg thiamin
		Chloride, m eq	210	137	308	4	+8 7	chloride i v
		Phosphate, m eq	148		107	34	+1 7	May 4, 100 gm glucose p o
		Nitrogen, gm	44 9		36 3	1 2	+1 8	No paralysis
May 6-10	XI	Sodium, m eq	189	137	294	2	+7 5	
		Potassium, m eq	255		178	25	+13 0	
		Calcium, m eq	177		43	111	+5 8	
		Chloride, m eq	211	137	310	2	+9 0	
		Phosphate, m eq	148		108	35	+0 2	
		Nitrogen, gm	42 5		37 7	1 2	+0 9	
May 10-14	XII	Sodium, m eq	194	137	317	9	+2 0	
		Potassium, m eq	276		240	34	+0 5	
		Calcium, m eq	183		32	110	+10 2	
		Chloride, m eq	203	137	329	6	+1 5	
		Phosphate, m eq	151		130	38	-4 2	
		Nitrogen, gm	41 6		38 7	1 1	+0 4	

fact It would require a significant loss of potassium and water from the serum, without subsequent replacement by another base, to produce a change in plasma volume which could be detected by present day methods. If the potassium loss were replaced by another base, such as sodium, no change in plasma volume would be detected.

Since it is believed that potassium does not migrate from the serum into the blood cells and until acceptable evidence is available describing its ultimate place of repose, conservative speculation may not be



TABLE IV  
Summary of certain balance data

DATE 1938	PERIOD	CONSTITUENT	DIETARY INTAKE	EXTRA DIETARY INTAKE	URINARY OUTPUT	FECAL OUTPUT	DAILY BALANCE	REMARKS
March 27-31	I	Sodium, m eq	182	137	270	9	+10 0	March 30, 100 gm. glucose p o Paralysis
		Potassium, m eq	265		212	37	+4 0	
		Calcium, m eq	167		48	231	-28 0	
		Chloride, m eq	188	137	287	4	+8 5	
		Phosphate, m eq	139		125	46	-8 0	
		Nitrogen, gm	42 3		38 5	2 8	+0 2	
March 31- April 4	II	Sodium, m eq	168	137	320	20	-8 7	April 5, 25 units insulin s c No paralysis
		Potassium, m eq	264		203	41	+5 0	
		Calcium, m eq	179		46	139	-2 5	
		Chloride, m eq	175	137	326	5	-4 7	
		Phosphate, m eq	141		137	42	-9 5	
		Nitrogen, gm	44 0		38 7	3 1	+0 5	
April 4-8	III	Sodium, m eq	191	137	263	22	+8 2	April 7, 100 gm glucose p o Paralysis
		Potassium, m eq	275		184	24	+16 8	
		Calcium, m eq	196		50	95	-12 7	
		Chloride, m eq	210	137	292	11	+11 0	
		Phosphate, m eq	144		140	30	-6 5	
		Nitrogen, gm	44 0		38 3	1 3	+0 8	
April 8-12	IV	Sodium, m eq	191	137	272	20	+8 0	April 12, 10 gm $\text{KH}_2\text{PO}_4$ p o April 13, 10 gm $\text{KH}_2\text{PO}_4$ , 100 gm glucose p o No pa- ralysis
		Potassium, m eq	273		211	45	+4 2	
		Calcium, m eq	182		44	156	-4 5	
		Chloride, m eq	189	137	298	13	+4 2	
		Phosphate, m eq	159		136	48	-6 2	
		Nitrogen, gm	44 6		37 0	2 0	+1 4	
April 12-16	V	Sodium, m eq	164	137	274	14	+3 2	April 17, 8 8 gm $\text{K}_2\text{C}_4\text{H}_4\text{O}_7$ p o April 18 7 0 gm $\text{K}_2\text{C}_4\text{H}_4\text{O}_7$ , 100 gm glucose p o No paralysis
		Potassium, m eq	215	146	326	43	-2 0	
		Calcium, m eq	159		30	118	+3 7	
		Chloride, m eq	177	137	325	4	-3 7	
		Phosphate, m eq	132	146	214	65	-0 2	
		Nitrogen, gm	40 0		38 9	1 4	0 0	
April 16-20	VI	Sodium, m eq	183	137	282	4	+8 5	April 20 11 minims adren- alin chloride 1 1000 r v No paralysis April 21 9 8 gm ( $\text{NH}_4$ ) $\text{H}_2\text{PO}_4$ p o April 22 9 8 gm. ( $\text{NH}_4$ ) $\text{H}_2\text{PO}_4$ , 100 gm glu- cose p o No paralysis
		Potassium, m eq	261	146	307	31	+17 2	
		Calcium, m eq	176		39	120	+4 2	
		Chloride, m eq	206	137	295	3	+11 5	
		Phosphate, m eq	150		134	42	-6 2	
		Nitrogen, gm	43 3		36 2	1 9	+1 3	
April 20-24	VII	Sodium, m eq	190	137	318	14	+1 2	April 20 11 minims adren- alin chloride 1 1000 r v No paralysis April 21 9 8 gm ( $\text{NH}_4$ ) $\text{H}_2\text{PO}_4$ p o April 22 9 8 gm. ( $\text{NH}_4$ ) $\text{H}_2\text{PO}_4$ , 100 gm glu- cose p o No paralysis
		Potassium, m eq	258		188	41	+7 2	
		Calcium, m eq	171		39	132	0 0	
		Chloride, m eq	202	137	326	5	+2 0	
		Phosphate, m eq	150		203	63		
		Nitrogen, gm	42 7	4 1	46 0	1 3	-0 1	

the vacuoles are small, but may occupy more than one-third of a fibrille. Apparently, they possess no membrane. The intra-muscular connective tissue is not infiltrated or hyperplastic. The number of sarcolemma nuclei (which average 6 per fiber) is not increased. The nuclei penetrate only rarely into the muscular substance. Nerve bundles when seen appear normal.

On longitudinal section the longitudinal and cross striations are distinct. Parallel to the longitudinal axis in almost all fibers are numerous holes, splits, tears, irregular spaces and lacunae. They have a clear glasslike appearance as do the vacuoles. Goldflam concluded with the statement that the pathological picture was distinctive and could be differentiated from Thomsen's myotonia and progressive muscular dystrophy.

Oppenheim (149) observed a waxy degeneration in a specimen of a deltoid muscle obtained at biopsy. Crafts (111) detected an increase in fibrous tissue, moderate hypertrophy and vacuolization of the fibers. The presence of vacuoles or unidentified droplets has been confirmed by Bornstein (101), Schmidt (79), Kaufmann (131), Zabriskie and Frantz (96) and Allott and McArdle (4).

#### PATHOGENESIS OF PARALYSIS

Many theories have been advanced to explain the pathogenesis of periodic paralysis. In the earlier literature the following have been offered. Post-malarial reaction [Hartwig (125), Gibney (122)], constitutional anomaly of skeletal musculature, auto-intoxication [Goldflam (29), Bernhardt (9)], recurring anterior poliomyelitis [Dana (19)], spasm of anterior spinal artery or diminution of blood supply to affected muscles [Westphal (176), Mankowsky (53), Holtzapfel (41), Schmidt (79)], accumulation of metabolites following exercise [Tsuji (89)], disturbance of function of the parathyroids and secondary hyper-calcemia [Neustadter (66), Shinosaki (85)], sluggish lymphatic circulation [Buzzard (12)], vagotonia [Schmidt (79)], hysteria [Dana (19)], increased adrenalin production [Neustadter (66)], disturbance of carbohydrate metabolism [Shinosaki (85), Yoshimura (93)], and congenital metabolism defect [Gardner (119)]. With but a few exceptions these theories have not been supported by acceptable laboratory data.

inopportune Following the injection of adrenalin in animals, a decrease in concentration of serum potassium is associated with an increased concentration of potassium in the liver It has been assumed that the deposition accompanies glycogenesis Similarly, during attacks of periodic paralysis in human beings, the liver may gain potassium at the expense of this constituent in the serum If one carries the analogy over completely from animal experiments, it is possible that the liver is enriched with glycogen as well as potassium Such a migration is consistent with the empiric observation that attacks of paralysis follow a meal with a high carbohydrate content

#### PATHOLOGICAL ANATOMY

Several biopsies from patients during or following attacks and a few autopsies on subjects who have died with paralysis have been reported The gross and microscopic findings are believed to contribute little to a precise understanding of the pathogenesis or etiology of the disturbance [Wexberg (92)] A comprehensive discussion of the morbid microscopic changes in the skeletal muscle of afflicted persons is given by Goldflam (33) Specimens of biceps muscle were obtained from 3 susceptible persons A translation of his findings is as follows "On cross-section, the muscle fibers have a polygonal shape, but with rounded corners The fibers are rather thick, of similar size, which varies between 45 and 90 micra Fibrilles are distinctly visible, more so than normally which creates on the surface a punctate appearance In many fibers the Cohnheim's fields are larger than normal The fibrilles are pressed apart by an amorphous mass which gives them the appearance of a sieve Each fibrille is visible at a low magnification and appears as a dot in the center of an amorphous mass This pathological process might be called rarefaction because the tissue actually appears rarefied The rarefaction embraces only the center of the muscle fiber while in the periphery the tissue is thicker than normal and the fibrilles appear compressed

In several fibers there are spaces which appear as vacuoles They are usually in the center of the fibers and have a round or oval shape Their content is mostly shiny or glasslike and not stainable Rarely, it is granular and stainable with carmine or eosin Still more rarely the content of the vacuoles consists of many small vesicles Usually,

recovery of function followed. These results suggested to the observers that either the curative action of potassium is central or that some substance is formed in the viscera by the action of potassium and is carried to the muscle to restore power. Additional evidence in support of a neurogenic defect in periodic paralysis was derived from experiments with acetyl-B-methyl choline chloride (meholyl). Return of function was perceptible within 8 minutes after 25 mg of the substance had been injected intraarterially. This was believed to be dependent upon the entrance of choline esters into the general circulation. A restoration of serum potassium without administration of potassium salts accompanied clinical improvement. The authors admit that this theory does not explain the loss of direct excitability of the muscle during paralysis. This interpretation, likewise fails to explain the local loss of muscle power from the cooling of one extremity as was shown by Zabriskie and Frantz (96).

Aitken et al. (2) investigated the disturbance of potassium exchange particularly with regard to the ingestion of sugar and the level of this constituent in the blood. They concluded that the decrease in serum potassium was not a compensatory physiological response to hyperglycemia but rather that the phenomenon involved a concomitant migration of potassium from the blood into the extra-vascular spaces. According to them this is a normal phenomenon but an increased sensitivity exists in patients subject to periodic paralysis.

The decrease in concentration of serum phosphate which accompanies the change in potassium (Table I) may be observed following an injection of adrenalin or insulin in normal as well as in persons susceptible to paralysis. Following the injection of either substance into animals, as the serum phosphate decreases the content of muscle and liver phosphate increases. It is assumed that similar changes occur in human beings. In intake and output studies of a patient with periodic paralysis Milhorat (54) observed that the excretion of phosphate in the urine paralleled that of potassium. The collected observations suggest that potassium and phosphate migrate together as the mono- and dibasic salts of potassium phosphate preceding or during an attack of periodic paralysis.

Lastly, the migration of potassium and phosphate may be initiated by an increased adrenalin content in the body fluids. This may

In recent years considerable insight into the mechanism of attacks has been gained and although as yet the evidence is not complete, it has assumed a definite shape. There appears to be little doubt that attacks of periodic paralysis are associated with a disturbance of the concentration of several chemical constituents of the body. In patients with the hereditary type of paralysis, the disturbance most likely is a manifestation of a constitutional chemical anomaly. In sporadic cases this may be an acquired character. In patients who develop paralysis during excessive assimilation of desoxycortico-sterone acetate, the chemical changes are induced.

The observations of Biernond and Daniels (10) and of Walker (222) that a diminution of serum potassium accompanied paralytic seizures are pertinent. Related constituents include serum phosphate, adrenalin content of body fluids and possibly glycogen content of the body. Although a diminution in potassium concentration appears to be the *sine qua non* of a paralytic attack, such a change may induce paralysis in a susceptible person only. A decreased concentration of serum potassium may be produced in normal persons by an injection of insulin or adrenalin without inducing demonstrable paralysis. Similarly, a lowering of serum potassium may be achieved in susceptible persons at times, without symptoms of periodic paralysis. For example, in our patient the potassium concentration ranged between 2.4 and 2.8 milliequivalents per liter in samples of serum after 3 glucose experiments, in none of which were paralytic symptoms observed. The conclusion seems warranted, that if paralysis develops in susceptible subjects it is accompanied by a diminution in concentration of serum potassium. On the other hand, a diminution in serum potassium may be observed in susceptible as well as non-susceptible persons without objective or subjective evidence of paralysis.

Confirmatory evidence that a change in concentration of serum potassium is intimately associated with the pathogenesis of paralysis was obtained by Pudenz and associates. They administered intravenously 1.0 gm. of potassium chloride to a subject during paralysis. Generalized motor function reappeared rapidly. The local effect of potassium salts administered parenterally was investigated next. 0.1 gm. of potassium chloride was injected into the brachial artery, following which the venous return was obstructed for 8 minutes. No

It was conceded that in all the reports which were reviewed a diagnosis of hysteria seemed justified, and that none of them appeared to be suffering from periodic paralysis. Although transient paralysis may accompany *grand mal* seizures of *epilepsy* [Higier (198)], the loss of consciousness and presence of convulsions should help differentiate this malady from periodic paralysis. *Acute anterior poliomyelitis* and *Landry's paralysis* affects similar age groups. Signs and symptoms of an acute infection and involvement of isolated muscles or muscle groups are helpful in reaching a correct diagnosis. *Infectious polyneuritis* has longer periods of weakness than does periodic paralysis. Facial paralysis and muscle atrophy are also frequent findings. In *tick paralysis* (184) the symptoms persist only as long as the parasite is attached to the host. *Recurrent facial paralysis* affects the nerves of the face and is not associated with a paraplegia. *Cerebral apoplexy*, *intermittent tonic muscular spasms* [Lenoble (202), Bennett (185)], *untreated Addison's disease*, *ophthalmoplegic migraine* [Clark (188)], *night palsy* [Ormerod (209)], *exhaustion paralysis* [Fere (193)] *general paresis*, *spasmodic paraplegia of syphilitic meningomyelitis*, *paroxysmal hemoglobinuria with paralysis* [Meyer-Betz (208)], *familial amaurotic ataxic paraplegia* [Stewart (216)], and *transient paralysis from postural hypotension* [Thomas (220)], need only be mentioned in passing, as in all these there usually are distinguishing signs and symptoms.

A differential discussion of the myopathies may not be dismissed as readily. Oddo and Darcourt (72) and Aring and Cobb (182) have called attention to the clinical similarity between periodic paralysis and other hereditary myopathies, i.e., myasthenia gravis, progressive muscular dystrophy, myotonia congenita, and paramyotonia congenita. Subsequent investigations may reveal that the pathogenesis of the muscle weakness in each condition is related. Symptoms of *myasthenia gravis* may appear intermittently as do those of periodic paralysis. In myasthenia gravis the muscles of the face and throat are usually involved but the skeletal musculature is not immune. Recovery from weakness follows potassium ingestion in either condition [Walker (222)]. The association of *progressive muscular dystrophy* and periodic paralysis in some patients is believed to be more than coincidence. This will be discussed in the next section. Symptoms from *myotonia congenita* begin to be disturbing in approximately the

result from the parenteral administration of insulin. Other procedures which increase adrenalin content of body fluid and which may induce attacks of paralysis include a high carbohydrate meal, strenuous exercise and thyrotoxicosis.

There are several points of similarity between the findings during attacks of periodic paralysis and in patients with Addison's disease following excessive assimilation of desoxycorticosterone acetate. A decreased concentration of serum potassium and phosphate, improvement in symptoms following potassium ingestion, an increase in volume of plasma and interstitial fluid, and acute cardiac dilatation have been observed in each condition. Furthermore, paralysis, indistinguishable clinically from hereditary periodic paralysis, may appear in the second group following a high carbohydrate meal.

#### DIAGNOSIS

A diagnosis of periodic paralysis usually is not difficult to make. The triad of paroxysmal flaccid paresis, loss of reflexes and loss of electrical excitability is unique and unmistakable. To these may be added unimpairment of mental function during attacks, precipitation of attacks by certain procedures such as ingestion of a high carbohydrate meal and administration of adrenalin, unimpairment of nervous sensibility, oliguria, decreased concentration of serum potassium, subsidence of paralysis following potassium ingestion, and absence of signs and freedom from symptoms between attacks.

#### DIFFERENTIAL DIAGNOSIS

There are several maladies which may be confused with periodic paralysis. *Hysterical paralysis* may be a presumptive diagnosis in patients during the first attacks of periodic paralysis [Samuelsohn (163)]. In hysteria, however, there are typical psychological abnormalities, the reflexes are usually increased and not decreased and sensory changes are often observed. The malady appears in a slightly older age group and has a much higher female to male sex ratio than does periodic paralysis. Because it was thought that patients with periodic paralysis might be incorrectly diagnosed as suffering from hysterical paralysis, more than 50 case histories of the latter, reported in the literature prior to 1900, were consulted by us

The occurrence of paralysis as a complication of *malaria* has not been studied methodically. There is general agreement in current literature that several of the cases of periodic paralysis which were reported in the last century [Cavaré (107), Romberg (160), Gibney (121) Hartwig (126)] were suffering concomitantly from malaria. The clinical description of the paralytic attacks is similar to that of hereditary periodic paralysis. It may be that the malarial infection merely acts as an inciting agent in persons susceptible to paralysis. A satisfactory explanation of the sensory disturbances which have been observed in patients with malarial paralysis [Stockwell (170)] is not forthcoming.

The association of *thyroid disease* and periodic paralysis is sufficiently frequent to give us reason to believe that in patients with both disturbances, the thyroid participates in the pathogenesis of the paresis. Enlargement of the thyroid has been observed in patients with sporadic periodic paralysis as well as in those with a family history of paralysis. Kitamura (230) in 1913 was the first to call attention to the combination. Since then more than thirty-five patients have been reported suffering from enlargement of the thyroid and periodic paralysis. Shinosaki (85) has reported fifteen patients, Tsuji (89) eight, Dunlap (114) four and Wexberg (92) three. It is conceivable that in some patients suffering from thyrotoxicosis, the muscle weakness (Basedow's paraplegia as it has been labelled by Mackenzie (204)) is an abortive type of periodic paralysis. We have made only one observation on this subject. Several years ago a patient with severe thyrotoxicosis and muscular weakness was studied in regard to base constituents in the serum. A concentration of serum potassium of 2.1 milliequivalents per liter was observed. Although this patient was very weak, it was not thought that she was suffering from periodic paralysis and the significance of the serum potassium level was not appreciated by us. According to our current interpretation, the muscular weakness might have been associated with the diminished concentration of serum potassium.

There are various other items which may be worthy of mention in a consideration of the coexistence of periodic paralysis and thyroid disease. A disturbance of carbohydrate metabolism may be observed in either condition. The precipitation of an attack of periodic



second decade of life as do those of periodic paralysis. Muscular inactivity, fatigue and exposure to cold aggravate weakness in myotonia. Quinine sulphate is beneficial in the treatment of symptoms in myotonia and in malaria which was an important inciting factor in production of periodic paralysis according to the earlier case reports. Beyond this, the analogy does not hold. In myotonia, the electrical reactions are increased and potassium ingestion is reputed to impede rather than improve muscular dysfunction.

#### ASSOCIATION WITH OTHER DISEASES

The association of periodic paralysis with other diseases will be discussed under 3 subdivisions: (1), coincidental association, such as tuberculosis and beri-beri, (2), diseases with which there may be a related pathogenesis, such as thyroid dyscrasia, over-treatment of Addison's disease and malaria, (3), nervous disorders, such as epilepsy, migraine, spinal muscular atrophy, progressive muscular dystrophy and progressive paraplegia.

*Tuberculosis* has been reported to have developed in a significant number of persons subject to attacks of paralysis as well as in their immediate relatives [Goldflam (28), Taylor (88), Biemond and Daniels (10), Mitchell (57), Skouge (168)]. The association is probably coincidental. A chronic infectious disease such as tuberculosis might lower the resistance in a person suffering from periodic paralysis and increase thereby the frequency of attacks. Beyond this, we can discover no related process characteristic of both conditions.

The development of *beri-beri* in patients subject to attacks of periodic paralysis is not so anomalous, at least not in the Orient where Shinosaki (85) observed several patients suffering from both diseases. It is presumed that the ingestion of large amounts of polished rice does not allow an adequate thiamin chloride intake and beri-beri follows. Similarly, a diet with a high rice content provides a high percentage of carbohydrate, which may be detrimental to persons susceptible to paralysis. This explanation of the association of beri-beri and periodic paralysis may be inadequate for the future although it appears to suffice for the present. An expansion of knowledge of the metabolism of thiamin chloride and carbohydrate may provide a more comprehensive explanation.

*Progressive muscular dystrophy* and *muscular atrophy* have developed in some patients several years after the onset of attacks of paralysis. The incidence appears to be higher in those with a family history of paralysis. Griedenberg was the first observer to call attention to the muscular development in a susceptible person which appeared to be out of proportion to the objective muscular strength. In three generations of one family, Biernond and Daniels (10) discovered that fourteen persons were subject to paralysis four of whom had in addition demonstrable muscular atrophy. In three of the patients, the atrophy was evident at the age of 11 only five years after the first attack of paralysis. In all, the atrophy was first noticed in the proximal portions of the extremities before it appeared in the distal portions. This sequence of appearance of muscular atrophy may be helpful in differentiating the muscle disorders of periodic paralysis from the spinal muscular atrophy of the Duchenne-Aran or the Werdnig-Hoffman type. Other instances of muscle disorders associated with periodic paralysis include *permanent paraplegia* [Mitchell (57)] and *astheric bulbar paralysis* [Collins (110)].

#### MORTALITY

There are more than thirty-five deaths reported in the literature which have been attributed to attacks of periodic paralysis. Thus contrary to many statements which have been made concerning the syndrome attacks may prove fatal. Hereditary and sporadic cases appear to be affected alike. A lucid mind is maintained generally up to the end. In some patients death followed the first attack. Goldflam reported one child that died during paralysis at the age of 9 months another of his patients died with paralysis at the age of 60. Concerning the pathogenesis of death respiratory paralysis [Holtzapfel (41) Neel and Jarlov (62) Mankowsky (53)] exhaustion of the muscles of the diaphragm [MacLachlan (52)] cardiac dilatation and decompensation [Zabnickie and Frantz (96) Šerko (82)], inhalation pneumonia [Shinosaki (84)] or inability to clear the trachea of aspirated vomitus [Atwood (5)] have been observed. At least four patients have died during venesections which had been recommended for diagnostic purposes or for treatment [Goldflam (30) Atwood (5)].

Two susceptible persons died during paralysis which was attributed to a superimposed thyrotoxicosis. One sufferer from hereditary

paralysis by a high carbohydrate meal has been mentioned. In patients with thyrotoxicosis, removal of sugar from the intestinal tract may proceed at a faster rate than in normal persons [Althausen (181)], while in animals, Coggeshall and Green (189) have produced rapid depletion of liver glycogen with ingestion of thyroid extract in spite of an adequate carbohydrate intake. Secondly, adrenalin is equally detrimental to patients with periodic paralysis and to those with thyrotoxicosis [Goetsch (196)]. Lastly, patients who develop typical periodic paralysis with enlargement of the thyroid are relieved of paralytic attacks following thyroidectomy. It seems reasonable to us to believe that in some patients with thyroid disturbance periodic paralysis appears as a symptom and may be related to excessive adrenalin production or sensitization to adrenalin by thyroxine.

The precipitation of paralysis during *excessive assimilation of desoxycorticosterone acetate* in patients undergoing treatment for Addison's disease has been discussed. A disturbance of carbohydrate metabolism exists in patients with Addison's disease as it does in patients with thyrotoxicosis. A retarded excretion of potassium by the kidneys in adrenal insufficiency, however, maintains a high concentration of potassium in the serum and protects against episodes of paralysis. Following the excessive assimilation of desoxycorticosterone acetate during treatment, increased excretion of potassium results and the concentration of serum potassium may be decreased to 2.5 milliequivalents or less. This is possible without restoration of the dysfunction of carbohydrate metabolism. This situation provides an appropriate setting for periodic paralysis.

Symptoms of *migraine* may appear in patients with periodic paralysis either during attacks or earlier in life before their onset [Higier (198), Shakhnowitsch (83), Janota and Weber (42), Ziegler (180), MacLachlan (52)]. Migraine may appear also in non-affected relatives of patients susceptible to paralysis. The largest series of such a combination has been reported by Holtzapple (41). In four generations of one family, thirteen members suffered from paralysis without migraine, a similar number suffered from migraine without periodic paralysis, while five suffered from paralysis as well as migraine. This writer interpreted an attack of migraine as the equivalent of an attack of paralysis. The co-existence of *epilepsy* and periodic paralysis is observed infrequently [Bornstein (102), Longo (51)].

to protect against mild attacks Early in this century the significance of the potassium effect was appreciated in the prevention of paralysis by Singer and Goodbody who advised potassium acetate, and by Buzzard (12) who advised potassium tartrate These early reports should not be overlooked now that potassium has been rediscovered as a substance useful in the care of patients with periodic paralysis

With the recently acquired knowledge of the importance of potassium salts in neuro-muscular disorders, larger amounts than were formerly used are now recommended Some patients require from 10 to 15 grams of potassium chloride per day as an effective preventive dose At other times or in other patients from 2 to 5 grams may be adequate [Herrington (35)] A portion of the total amount ingested each day should be taken at bedtime Until additional evidence is available it is believed that ingestion of potassium salts should be maintained indefinitely In the absence of renal insufficiency, no harmful effects are to be anticipated from continuous daily therapy.

An inexpensive method for preparation of potassium chloride is a 25 per cent aqueous solution, one teaspoonful of this solution contains approximately 1 gram of salt An aqueous solution is less irritating to the gastrointestinal tract than are compressed tablets or gelatin capsules which contain potassium chloride The use of enteric coated tablets is a luxury

#### TREATMENT

Potassium chloride is as effective in the treatment of attacks of periodic paralysis as it is in the prevention of them [Gardner (119), Aitken et al (2)] Oral administration of from 2 to 10 grams in an aqueous solution usually is adequate In patients unable to swallow, this may be administered by stomach tube Experimentally, potassium chloride has been injected intravenously [Pudenz et al (77)] with prompt subsidence of paralysis

#### SUMMARY

Periodic paralysis as a symptom complex is discussed The characteristic triad of the syndrome includes periodic paralysis, loss of reflexes and loss of electrical excitability There is no loss of consciousness The syndrome appears as an hereditary trait in certain

periodic paralysis was burned to death in the Russian Army by fellow soldiers because he was thought to have been a malingerer. Isolated instances are reported of patients dying with paralysis and an infection such as acute otitis media, pneumonia, puerperal fever and acute entero-colitis. Since periodic paralysis has a mortality of approximately 10 per cent, a guarded ultimate prognosis should be given.

#### PREVENTION

In periodic paralysis as in many other afflictions, a state of good health appears to be an important factor in prevention. Particular attention should be paid to the prevention of acute infections and incipient symptoms of diseases with which periodic paralysis is associated. Avoidance of strenuous exercise, prolonged rest in bed, exposure to cold and dampness, and emotional excitement are important. Gestation appears to exert a favorable influence on the incidence of attacks [Janota and Weber (42)]. In one patient studied by Cousot (17), pregnancy was followed by complete freedom from seizures.

Regulation of the carbohydrate content of the diet should be easy to execute and is one of the essential stones in the foundation of prevention. Since a high carbohydrate intake is a frequent incitor of acute attacks, avoidance of sugar debauches is theoretically sound and practically effective. Not more than 100 grams of carbohydrate should be ingested at one meal. A 6 meal a day regimen may be useful for those patients who are particularly susceptible to carbohydrates. Candy, preserves, and pastries should be ingested in temperate quantities.

The protection afforded by the ingestion of potassium salts may not be complete, but the frequency of mild attacks is reduced and the severity of the major ones is diminished. Potassium bromide was probably the first potassium salt to be recommended for periodic paralysis. Goldflam (30) commented on its therapeutic efficiency in 1891, while in 1904 Holtzapple (40) stated that he had used it successfully for 18 years in the treatment of one of his patients. The indications were probably empiric and greater therapeutic effect was attributed to the bromide than to the potassium ion. The quantities recommended, however, were large and contained sufficient potassium

The following morning there was normal function in the arms, but the legs were weak. By noon the weakness had disappeared. During the intervening 5 years he had many similar attacks in the night. The attacks occurred as often as four a week and as infrequently as every 6 months. The severe attacks lasted as long as 12 hours. During paralysis, the patient was able to void and defecate if carried to the bathroom. The only prodromatal symptoms were fatigue on the evening before the attack and a desire to retire early.

On physical examination he appeared undernourished. He had an adenoid facies and prominent frontal bosses. He had a lethargic appearance when he was in repose. The heart and lungs were negative. The muscle groups of the arms and legs appeared small for a body of 12. The neurological examination was negative. The urine examination and blood cell counts were normal. The blood Hinton reaction was negative. The basal metabolic rate was +26 percent. The cerebrospinal fluid dynamics were normal. No cells were seen. The total protein was 20 mg per 100 cc., sugar was 66 mg per 100 cc. The gold sol curve was 0000000000. Electrical reaction to faradic and galvanic current was normal. The x-rays of the skull and chest were normal.

He was transferred to the metabolism ward where he was observed for more than two months. On March 19, 1938 he was given 100 grams of glucose p o. Three hours later he began to feel weak, lost the coordination of his legs and the strength of his grip. Four hours after the glucose was given he was helpless in bed. The deep reflexes were present but less active than on admission. No muscle contractions were elicited with faradic current. The galvanic current produced slight contractions in the right arm, no contractions in the left arm or legs. 10 grams of potassium chloride was given by mouth. Two hours later he was able to move about normally and experienced no after effects.

A constant dietary regimen was begun March 23, 1938, and continued for approximately 7 weeks. The study was divided into 13 periods of 4 days each. Food was procured in  $\frac{1}{4}$  day batches and an aliquot of each batch was analyzed for water, sodium, potassium, calcium, chloride, phosphate and nitrogen content. A preliminary  $\frac{1}{4}$  day period was used as a control to allow the patient to come into nitrogen and salt equilibrium. Urine and stools were discarded in this period. Beginning with the fifth day of the metabolic regime 12 periods were obtained. Stools were collected and partitioned into  $\frac{1}{4}$  day periods and analyzed for the same constituents as the diet. Urines were collected and partitioned into 2 $\frac{1}{2}$  hours

families, sporadically in susceptible persons, in association with thyroid disease and malaria, and following a high carbohydrate meal during excessive assimilation of desoxycorticosterone acetate in the treatment of Addison's disease. In all instances, except for the hereditary cases, there is a strong predilection for the male sex. The tendency to periodic paralysis may appear in families as a dominant or as a recessive trait. There may be several factors which incite attacks. They include strenuous exercise and high carbohydrate ingestion. Both may be associated with increased adrenalin production.

A constant finding during attacks of paralysis is a decrease in concentration of serum potassium. Experimental data indicate that the potassium migrates from the serum into the extra-vascular areas, presumably into the intra-cellular spaces. The pathogenesis of the syndrome is thought to be intimately associated with this redistribution of potassium. Subsidence of paralysis is accompanied by restoration of the concentration of serum potassium. It is believed that periodic paralysis is a syndrome which may be observed under various circumstances, but whatever the association it is incited by the same underlying metabolic dysfunction. It is quite possible that many persons are susceptible to periodic paralysis under certain circumstances. If this assumption is correct, periodic paralysis may be interpreted as an abnormal physiological response just as hyperventilation tetany and heat cramps are exaggerated physiological responses.

#### PROTOCOL

C G, M G H Unit No 111014, a white American-born boy, aged 12, was admitted to the hospital on March 14, 1938, complaining of periodic attacks of weakness and paralysis since the age of 7. A diligent interrogation of the patient's family failed to reveal any history among known relatives of a similar disorder. The mother and maternal grandmother suffered from migraine. The patient had chickenpox, measles, mumps without any serious sequelae. His mother believed that he had been underweight for some time and was never as robust as were his friends.

He awoke in the middle of the night during his seventh year and was unable to move any extremity. Movement of the head and neck was limited. There was no disturbance of sensation or loss of sphincter control.

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F. S. Coombs and Messrs. W. V. Consolazione and L. J. Pecora who aided in the laboratory studies.



specimens Each day's output was analyzed for ammonia, total base, titratable acid, creatine and creatinine in addition to the constituents determined in diets and stools The pH of the urine was measured also

Several experimental procedures were investigated during this time They are enumerated in the remarks of the various tables 100 gm of glucose was successful in inducing an attack on 3 subsequent days No attacks were induced if the ingestion of glucose had been preceded on one or more days by ingestion of potassium phosphate, potassium citrate, ammonium phosphate or thiamin chloride No attack was induced by 25 units of insulin or 11 minims of adrenalin, 1/1000 dilution

The patient was discharged after the completion of the metabolic studies He was advised to restrict his carbohydrate intake and to take from 2 to 4 grams per day of potassium chloride dissolved in water The following 24 months he gained 32 pounds of weight and took on the appearance of a normal healthy boy On several occasions in this interval, he stopped the ingestion of potassium chloride either experimentally, according to our suggestion, or because his domestic supply was exhausted An attack of weakness or paralysis usually followed within a few days Resumption of the salt was associated with freedom from symptoms Following Christmas dinner on one occasion and a children's party on another, he developed paralysis in spite of the ingestion of potassium It was evident that from 2 to 4 grams of potassium chloride would prevent attacks under normal conditions, but not after excessive carbohydrate intake

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During the preparation of this manuscript, an unsuccessful attempt was made to peruse all of the papers in the complete bibliography in modern medical literature of periodic paralysis There are included, therefore, several case reports of periodic paralysis from journals that were not available in this country at the time the review was compiled

Following the usual bibliographical data, the number of patients and their respective sexes are appended when the information has been given It is hoped that there had been no significant duplication of cases Particular attention has been given to the possibility of two writers describing, independently, one patient or one writer compiling several articles about the same group of cases When the sum of the cases enumerated according to sex does not reach the total cases reported it is because the sex was not mentioned in each instance <sup>2</sup>

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## WEIL'S DISEASE

### A COMPLETE REVIEW OF AMERICAN LITERATURE AND AN ABSTRACT OF THE WORLD LITERATURE SEVEN CASE REPORTS

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#### INTRODUCTION

Weil's Disease is a specific infection caused by *Leptospira icterohemorrhagiae* and characterized by a sudden onset with profound



Report (1) uses the term "Leptospirosis icterohemorrhagica" with some justification but it is a bulky term which tends to be shortened to "Leptospirosis", this latter being incorrect because there are other strains of *Leptospira* which produce disease in man. We feel that with a full understanding of the nature of the disease "Weil's Disease" is a simple and adequate terminology which should be retained. It signifies the acute systemic infection caused by *Leptospira icterohemorrhagica* and no other entity.

#### AMERICAN AND WORLD INCIDENCE

Inada (4) in 1916 reported that a spirochete was the causative agent and Noguchi (7) classified the organism and named it *Leptospira icterohemorrhagica*. Packhamian (47) has unearthed the interesting fact that Stimson (46) discovered a spirochete in the organs of a person dying of what was then thought to be yellow fever. He called this organism *Spirillum interrogans* because of its shape. Wadsworth (8) in 1922 first recognized a case of Weil's Disease in this country and proved the diagnosis. In 1935 Jeghers (5) reviewed the American literature and found eleven reported cases. In 1937 Packhamian found 32 proved cases (47). Eighteen of these were from other observers and 14 were his own. He does not give any of the details of these cases. Since that time there have been reported about 35 (37 56 17 44 95 24 97 98) others making a total to date of 67 cases (including our own seven excluding Hawaiian cases).

In 1939 there appeared a review from the Netherlands in which 374 cases were exhaustively studied (1). The number reported in England (9) France (10) and Germany (11) runs well over a thousand. Large numbers of cases are reported from Japan (26). It has been found to be relatively common in Denmark (12) Austria (13) Egypt (14) and parts of South America (15). Weil's Disease has been reported from nearly every civilized country. (Walch-Sorgdrager (1) lists 46 countries in which the disease has been described.) It has been described and treated by Japanese observers in the Philippines more frequently than in the United States (76 102). Why then has it been rarely diagnosed and more rarely proved in this country?



prostration, aching muscular pain, a high fever, and frequently with the subsequent development of jaundice, evidence of renal failure, and a hemorrhagic diathesis

In our study of this disease, we have been gratified to find that after the identification of the first case, the hospital staff have been able to make the clinical diagnosis of Weil's Disease with comparative ease, yet there has been no over-enthusiasm resulting in unwarranted diagnosis

In this presentation we have borrowed freely from a great mass of foreign literature. We have no first-hand knowledge of the disease as it exists in Europe and the Orient and have used the material from the world literature only to add scope, emphasis, and clarity to the information we have derived from a study of our own and other American cases

### HISTORY

Prior to Weil's (3) classic description in 1886, a few epidemics of jaundice were described which, in some respects, resemble the disease as we now recognize it (1). In 1800, Larrey (2) noted certain cases with jaundice, hemorrhage, injected conjunctivae, and renal failure, among French soldiers in Egypt. Packhamian (47) believes some of the jaundice seen in the American Civil War was probably of a similar nature. In 1886, Weil (3) described the disease in detail, differentiating it from other types of acute jaundice, and reported four cases in young men, all of whom got well. These four cases were characterized by sudden onset with severe shaking chills, prostration, jaundice, hepatomegaly, splenomegaly, hemorrhagic tendency, and evidence of renal failure.

### NOMENCLATURE

As we know the disease today, the severe shaking chill is uncommon (though chilly sensations are frequent), and splenomegaly is absent except in cases with a pre-existing enlargement of the spleen.

Because of these differences, many authors have suggested other names for the disease. "Spirochetal Jaundice" has been suggested (4), but it is less satisfactory than "Weil's Disease" because nearly fifty per cent of the cases show no jaundice. The League of Nations

cats (18) pigs (21) foxes (23), and horses (22). Students of the subject (1, 5) agree that the vast majority of known cases come from direct contact with the excreta of rats. The causative organism will live for a period longer than three weeks (6) in stagnant water which is neutral or slightly alkaline. In the Netherlands it has been shown (1) that 91 per cent of the cases come from contact with water and only 9 per cent from those whose occupations necessitate the frequent handling of rats. It has been shown that water infected with the excreta of spirochete-carrying rats may infect man either through abrasions on the skin (49) through the gastro-intestinal tract (4)—probably unusual because the normal gastric acidity destroys the *Leptospira*—through the nasal mucous membrane (5), or through the mucous membrane of the conjunctivæ of the eye (77). The older theory resulting from experiences with jaundice in the trenches during the World War namely that the *L. icterohemorrhagica* will pass through the unbroken skin is probably not correct.

Most of the cases reported in this country have been in persons whose occupations demanded working in wet places where rats were common (1, 44). Cutters and cleaners of fish are frequently infected. The organism grows well in fish skins. It has been reported in miners who work in wet mines (46) sewer workers (38) tunnel diggers and possibly in those who have been swimming in contaminated water (41). Two cases have been reported (24, 17) of infection via infected dogs. It has been reported in butchers (39) and in a veterinarian (17). In many of the American cases the source of infection is unknown.

Studies in Europe indicate that one may expect to find the disease in all rat-infested places where water is permitted to remain for a period of time (7, 31, 6). In Rotterdam (1) 71 cases have been reported from accidental falling into dirty canals and also from swimming in one of the local swimming pools in which the daily exchange of water is not sufficient to keep the pool clean. In Aberdeen it is known as the fish-workers disease (53). The disease was demonstrated in cooks during the great war (28) and it is not uncommon in sugar-cane cutters in the tropics (29). In Japan the disease is common among rice field workers (26) and it has been found that adding an acid fertilizer to the fields before flooding will materially cut down the incidence of the disease (27). Many cases have been reported

A study of American rats (the common vector) has shown that they are infected with the same frequency as European rats (16). The occupations in which it is commonly found in Europe—sewer workers, fish cleaners, and workers in damp mines, ditches, and tunnels—are common occupations in America. In general, our laws do not provide for a more satisfactory elimination of rats than is carried out in France, England, and Germany, though it must be admitted that our sewage disposal systems make it less likely that the excreta of sewer rats come into contact with those employed to maintain the sewer systems. There is no reason to suppose that we are an immune race of people.

The reasons for this discrepancy are probably numerous. Meyer (17), in San Francisco, has found that when Weil's Disease is carefully searched for, it is not difficult to find. American textbooks of medicine have described the disease poorly, emphasizing chills and splenomegaly, which are rarely present. American City and State Health Laboratories are not equipped to establish the diagnosis. Most doctors in this country have felt that it is a rare or unknown disease here, and consequently rarely consider it in their differential diagnosis. Few physicians are aware that only 50 per cent of the cases have jaundice. Finally, in those few laboratories in which astute clinicians have attempted to prove the diagnosis, they have frequently failed because they have not been familiar with the precautions which must be taken in order to establish the diagnosis in each of the three distinct stages of the disease.

We feel that Weil's Disease is probably not rare in this country and since, untreated, it has a mortality rate of about 30 per cent in jaundiced cases, we feel justified in again calling attention to a disease described 54 years ago. Also, we feel that better recognition of the disease is desirable because therapy is simple and effective, but will not become easily available until the true incidence and importance of the disease is better realized.

#### MODE OF INFECTION

The *Leptospira icterohemorrhagiae*<sup>1</sup> is found in the excreta of better than 10 per cent of adult common gray rats (5). It has also been found not infrequently in dogs (19), and is known in field mice (1),

<sup>1</sup> For detailed description of the organism, see section on diagnosis

## SEASONAL INCIDENCE OF THE DISEASE

The vast majority of the cases reported in this country occurred during the summer months June July August, and September. A similar maximal incidence in the months of July, August and September is reported in Europe (1)

## CLINICAL FEATURES OF THE DISEASE

The clinical course of the disease may be divided into three stages which run one into the other without a sharp line of demarcation. These stages are important for diagnosis, and a thorough knowledge of the features of each stage is essential if one wishes to apply correctly the various diagnostic procedures.

The best evidence for determining the incubation period of the disease is found in accidentally infected cases among laboratory workers. Inada reports five to seven days (4). In 56 carefully selected cases Walch-Sorgdrager (1) found a range of from  $\frac{1}{2}$  to 19 days with a mean incubation period of 9.5 days in all cases whether icteric or non-icteric. Jeghers (5) quoting Schüffner, found the mean to be 10.3 days. The length of the incubation does not appear to be of prognostic significance.

*First stage* The first stage is called the septicemic stage of the disease and it lasts from two to nine days usually five (1). In this stage the spirochete is circulating in the blood stream and can be found in blood serum or plasma. During this stage there are no specific antibodies in the blood and the organism is not excreted in the urine to any appreciable extent. The first stage includes the onset of the disease and all signs and symptoms up to and inclusive of the onset of jaundice. In non-jaundiced cases it may be said to last as long as spirochetes are demonstrable in the circulating blood.

The onset of the disease is sudden (even in mild cases); not infrequently the patient can name the exact hour at which he became ill. Characteristically there is an abrupt onset of severe headache usually frontal but occasionally bitemporal or occipital often associated with chilly sensations and severe prostration. Occasionally (seven American cases) there is a severe shaking chill but this is by no means a constant finding. One of our cases—No. 2—had an initial chill. Muscular aching especially of the muscles of the calves of the legs

from drinking contaminated water (30), although these are not all authentic. Fish workers (31) and sewer workers (99) are commonly infected in London and Paris. In England (25), Weil's Disease is now considered an occupational disease in certain industries in which wet floors are unavoidable, and industrial compensation has been paid in a fatal case. It has now been recognized as a compensable occupational disease in fish workers in New York (37). One case has been reported of transmission via copulation (103), and one has been reported of intrauterine infection of the foetus (102). However, man-to-man infections must be rare in spite of the fact that virulent organisms may be excreted in the urine for weeks.

#### AGE AND SEX DISTRIBUTION

Of the reported cases in this country, more than 90 per cent were males. This striking male preponderance is also common in Europe (1) and in Japan (26).

In a series reported from the Institute for Tropical Hygiene in Amsterdam (1) (363 cases), 323 were males and 40 were females. Smith and Davidson (6) have shown that this is not a sex-linked susceptibility, but purely an occupational difference. In 210 fish workers tested, there were many more women with the disease than men, and in that group the proportion of women to men in the industry was 10/3. The ratio of infected workers, women to men, was  $19\frac{1}{2}/3$ .

Weil's Disease is rare in children. One case (24) has been reported in this country in a child aged three, and in that instance the immediate contact came from a dog and not directly from rats\*. Hindle and Brown (31) described a small epidemic in children in England. Apparently intrauterine foetal infection can occur (103). Walch-Sorgdrager (1) reports the following age incidence in 370 collected cases.

Age 1-10	11 cases
10-40	210 cases
40-60	49 cases
60 and over	15 cases
Age unknown	85 cases
	<u>370 cases</u>

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\* The authenticity of this case has been questioned (56)

nuchal tenderness and rigidity The French (91) describe true opisthotonos, but this symptom is rare

Leukocytosis is present from the onset, and is usually between 14,000 and 20,000, with a marked increase in young polymorphonuclear leukocytes Myelocytes are not uncommon Early there is slight anemia, and even though the hemorrhagic tendency is prominent, the platelets and prothrombin time are normal The urine is scanty in amount and may show only moderate amounts of albumin, or may show all the abnormalities of acute glomerulo-nephritis or the nephrotic syndrome Early in the disease bile and urobilinogen are absent The sputum, when present, is frequently foamy and may contain bright blood Only mouth contaminant organisms are found In the two of our cases with sputum, both were bloody and neither contained a pneumococcus which could be typed, or demonstrable spirochetes The vomitus contains ingested food and bile It usually gives a positive benzidine reaction, but gross blood is not found unless there is associated epistaxis or hemoptysis The stool is normal but occasionally may give a positive guaiac test The spinal fluid has been examined infrequently in this country, and not as routinely as might be desired in Europe In most cases there is a moderate increase in protein, the Pandy reaction is positive, and there is an increase in cells The range may be 50 to 1,000 cells, of which approximately 50 per cent are polymorphonuclear leukocytes, and 50 per cent lymphocytes The spinal fluid pressure is normal or elevated The chlorides and sugar have not been studied sufficiently to draw conclusions A pellicle is formed in many cases The spirochetes have been cultured from the cerebro-spinal fluid by European observers (91-94), but this finding has not been verified in this country\* We do not doubt that they are present The blood urea nitrogen is elevated and increases rapidly as the disease progresses Blood urea nitrogen levels of 50 to 100 mgm per cent are common, and we have seen them reach 150 mgm per cent The blood sugar and chlorides are normal Unless there is complete anuria, the CO<sub>2</sub> combining power is not markedly abnormal When anuria occurs evidence of profound acidosis may be present

In this stage, the *L. icterohemorrhagiae* may be found by direct

\* A recent personal communication indicates that leptospiral meningitis does exist in this country and will be described soon

the back, and the extraocular muscles, is pronounced, and there is tenderness on slight pressure over the calves. Anorexia quickly becomes pronounced, and frequently nausea and vomiting are persistent and severe symptoms. Abdominal muscle pain may be associated with vomiting, and the condition may be difficult to distinguish from an acute "surgical abdomen." Cough and hiccough are common and frequently associated with sputum which may be bloody, suggesting pneumonia, and this may actually be present.

Physical examination in the first stage of the disease reveals a high fever ( $102^{\circ}$  to  $106^{\circ}\text{F}$ ), a pulse which is full and fast but not infrequently less rapid than would be expected from the temperature, normal or rapid respiration, and normal or somewhat low blood pressure. The patient appears acutely and seriously ill. The skin is hot and dry. Herpes is unusual and when present is usually hemorrhagic. Uncommonly one may find a rash. It usually does not appear until the second stage. The ocular conjunctiva is moderately injected, frequently suggesting "pink eye." The pharynx is slightly injected, though the patient is usually unaware of a sore throat. Our Case No. 1 had severe sore throat as his presenting complaint. Lymphadenopathy is conspicuous by its absence. The chest and lungs may be normal or may show evidence of patchy pneumonic consolidation. In the latter cases the rales are more moist than those found in typical lobar pneumonia, even though the sputum frequently appears typical of pneumococcus infection. The heart shows little save tachycardia. Rarely a pronounced bradycardia may appear. Even in the first stages, evidences of capillary damage may appear as petechial and ecchymotic hemorrhages scattered over the body, and small hematomas after vein puncture are common. The abdomen is soft and flat. Tenderness may be present, but careful examination reveals that it is muscle wall tenderness and not the result of peritoneal irritation or inflammation. Peristalsis is present and normal. Rarely, when the hemorrhagic tendency is severe, peritoneal petechial hemorrhages may occur, giving all the evidences of an acute abdomen, however, the presence of purpura elsewhere usually indicates the cause. The muscles of the legs and back are tender. Not infrequently there is muscle tenderness in the neck, and slight or marked nuchal rigidity. The deep and superficial tendon reflexes are diminished. Kernig's sign may be positive in those cases with marked

nuchal tenderness and rigidity. The French (91) describe true opisthotonos, but this symptom is rare

Leukocytosis is present from the onset and is usually between 14 000 and 20,000, with a marked increase in young polymorphonuclear leukocytes. Myelocytes are not uncommon. Early there is slight anemia and even though the hemorrhagic tendency is prominent, the platelets and prothrombin time are normal. The urine is scanty in amount and may show only moderate amounts of albumin, or may show all the abnormalities of acute glomerulo-nephritis or the nephrotic syndrome. Early in the disease bile and urobilinogen are absent. The sputum when present is frequently foamy and may contain bright blood. Only mouth contaminant organisms are found. In the two of our cases with sputum, both were bloody and neither contained a pneumococcus which could be typed, or demonstrable spirochetes. The vomitus contains ingested food and bile. It usually gives a positive benzidine reaction but gross blood is not found unless there is associated epistaxis or hemoptysis. The stool is normal but occasionally may give a positive guaiac test. The spinal fluid has been examined infrequently in this country and not as routinely as might be desired in Europe. In most cases there is a moderate increase in protein, the Pandy reaction is positive, and there is an increase in cells. The range may be 50 to 1,000 cells, of which approximately 50 per cent are polymorphonuclear leukocytes and 50 per cent lymphocytes. The spinal fluid pressure is normal or elevated. The chlorides and sugar have not been studied sufficiently to draw conclusions. A pellicle is formed in many cases. The spirochetes have been cultured from the cerebro-spinal fluid by European observers (91-94), but this finding has not been verified in this country\*. We do not doubt that they are present. The blood urea nitrogen is elevated and increases rapidly as the disease progresses. Blood urea nitrogen levels of 50 to 100 mgm per cent are common and we have seen them reach 150 mgm per cent. The blood sugar and chlorides are normal. Unless there is complete anuria the CO<sub>2</sub> combining power is not markedly abnormal. When anuria occurs evidence of profound acidosis may be present.

In this stage the *L. icterohemorrhagic* may be found by direct

\* A recent personal communication indicates that leptospiral meningitis does exist in this country and will be described soon.



dark-field examination of the blood, or may be cultured from the blood or spinal fluid in suitable media. The technique for dark-field examination is described subsequently.

The symptoms and signs increase in severity as the disease progresses, and the temperature remains high throughout the first stage of the disease. On about the fifth or sixth day of the disease the temperature falls abruptly to near normal, and jaundice appears. Even though the patient's temperature chart looks as though he ought to be better, it is obvious from his appearance that his condition is worse. Thus is the second stage ushered in.

*Second stage.* The second stage has been called the "icteric" stage, an unsatisfactory term, because not all cases are icteric. Jegher's (5) term "Toxic Stage" is hardly suitable, because in the non-icteric mild groups, the symptoms of profound toxicity are no more apparent than is the icterus. When one considers the symptoms and signs of the worst fatal case in this stage and compares them with those of the mildest non-icteric case, they have little in common. For practical purposes the non-icteric group of cases has no second stage, except in those patients with severe meningitis described by the French (91). They go directly into convalescence. Exclusive of those cases which are fatal before the 10th or 12th day, all cases have a period of a week or more during which the organism disappears from the blood, appears in the urine, and specific agglutinins and lysins begin to appear in the blood. Schuffner's (19) dictum that "Where there is no jaundice there is no mortality," applies generally except in the so-called "Spirochétose méningée pure" (57, 91), which will be discussed later.

Therefore, we suggest the use of the simple term, *second stage*, to signify that stage of the disease in which the normal mechanisms of the body either win or lose the battle against the invading spirochete.

Inada (4) states that jaundice appears in the middle of the first week. Strasburger (78) gives from the third to the ninth day inclusive. Martin and Pettit (32), in a careful study of 132 cases, found that it appeared most frequently on the fifth day, the range being two to ten days. In our seven cases, jaundice appeared on the third, fourth, sixth, and ninth days.

The intensity of the jaundice increases rapidly and may vary be-

between just detectable icterus and a profound, intense bright orange-yellow jaundice. Icterus indices as high as 325 have been found in our cases.

Only one non-icteric case has been reported in this country (17)\* in Europe however as students of the subject became more familiar with the disease the incidence of non-icteric proven cases rose rapidly, until at the present time analysis of large collected groups of cases shows that not more than 50 per cent ever became jaundiced (1). A few authors find the number even lower. The following table from Valch-Sorgdrager shows the jaundice incidence observed by a number of authors.

	NUMBER OF CASES	NUMBER WITH JAUNDICE	PER CENT WITH JAUNDICE
Wido, Wani	56	23	41
Stokes, Ryle Taitler	100	60	60
Strasburger	26	23	88.5
Thower	27	27	100
Lorando	35	25	71
Netherlands (Institute Tropical Medicine)	342	205	60.7
(Kramer, Rotterdam)	73	28	38.3
Davidson, Campbell, Roe, and Smith	15	11	78.3

Apparently, familiarity with the disease, available diagnostic methods, and intensity of search determine the percentage of non-icteric cases diagnosed.

Early in the second stage the evidence of renal failure becomes pronounced. Oliguria may become marked, and occasionally anuria develops. The urea retention increases and evidence of renal acidosis may appear.

The hemorrhagic tendency becomes more apparent. Purpuric and ecchymotic spots on the skin are common and they may appear in the mucous membranes of the mouth, the nose, and the vagina. The conjunctivae may show petechial hemorrhages, and scleral ecchymosis may appear.

Vomiting usually stops early in the second stage and complete anorexia is common.

\* There are probably two or three others (56).

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Peristalsis is diminished. Rarely, there is moderate costovertebral tenderness when the hemorrhagic tendency is marked, possibly indicating sub-capsular renal hemorrhage. Tenderness in the muscles of the back and calves is less pronounced, and all of the tendon reflexes become diminished.

The laboratory data show a high and rising icteric index and blood urea nitrogen. The white blood count which was between 10,000 and 14,000, may remain the same, frequently, however, with falling temperature and rising icterus, the white count may go up to leukemic levels of 30,000 to 50,000, and show large numbers of young granulocytes. The red count is usually somewhat lower than it was initially. We have not noted the fall in platelets and failure of clot retraction described by Pagniez (69). Profound anemia in the second stage is rare. The urine is scanty in amount, deeply jaundiced, and shows increased amounts of albumin, cellular debris and casts. Bile is found in the urine in large amounts. The stools are light in color but rarely acholic (our case No. 1 had acholic stools for a few days). The  $\text{CO}_2$  combining power is normal or low. The blood sugar is unaltered. The spinal fluid remains unchanged except for the development of a yellow tinge which may be differentiated from true xanthochromia by allowing it to stand in a bright light. If the color is due to jaundice, it will fade. The red-cell sedimentation rate is elevated moderately, and the prothrombin time early in this stage is normal.

In the fatal cases, death usually occurs between the 9th and the 16th day (1). The Japanese fatality rate in untreated cases was early reported as 30 per cent (4). In larger series of cases in Europe, it ranges from 11.9 per cent (1)—some of these were apparently serum-treated—to 60 per cent (4), in the most severe epidemics. In this country the mortality rate to date is about 30 per cent.

Death may occur as a result of renal failure (1), combined renal and hepatic failure, cardiac failure (71), as a result of the hemorrhage, from severe toxemia, or as a result of a complicating terminal pneumonia (our case No. 5). Adrenal hemorrhages are common at autopsy, but there is no adequate evidence of an adrenal death. The meningitis rarely, if ever, kills. A few rare complications have been described, which may be fatal: thus myocarditis has been described

Early in the second stage of the disease, the temperature may be quite high, 103° to 104°F, with concomitant elevation of the pulse, but more frequently the temperature is low—98° to 101°F—and the pulse rate is relatively high, 100 to 130. The temperature-pulse ratio is frequently reversed from the typhoid-like form frequently seen in the first stage. The respirations may be normal but are often increased in rate and there may be prolonged expiration indicative of acidosis.

The patient appears extremely toxic, and is semi-comatose. Frequently he lies motionless, staring at the ceiling and responds slowly to questions. Again, he may be agitated and delirious, or, he may be motionless except for his eyes, which search the room constantly, suggesting visual hallucinations. Occasionally, although the patient appears to be completely disoriented, he may respond fairly intelligently to command but his responses are slow. Usually the complaint of headache, which was apparent in the first stage, is gone, and he may have no specific complaint.

Jaundice is easily apparent. Evidence of pruritus is rare. There may be hemorrhagic herpes labialis [25 per cent of cases (70)], crusted blood in the nose is common. The conjunctivitis is much less apparent. A measles-like or scarletinaform rash has been described (1) in about 10 per cent of the cases in Europe. Apparently it is not prominent in American cases. It may have been present in our Case No. 4. Nuchal rigidity is usually absent, and there is little or no lymphadenopathy. The chest may be quite clear or may show evidence of patchy consolidation, usually in one of the lower lobes. The heart is normal in size, and the rate is quite rapid. Ectopic beats are not uncommon, pericardial friction may appear. The heart tones are less distinct than previously, they are muffled, and of poor quality. Systolic murmurs may appear. Unless elevated by co-existing hypertension, the blood pressure tends to be at low normal levels. The venous pressure is not elevated, and there is no evidence of congestive failure but there may be meagre evidence of peripheral circulatory disturbance such as patchy cyanosis and cold extremities.

In the abdomen, the liver is obviously enlarged, and, not uncommonly, is moderately tender. The spleen is usually *not* palpable. Moderate abdominal distention due to a low grade ileus is common.

titers are demonstrable. The serological technique of Schuffner (19) is accepted by Meyer (17) and Packchaman (47) as highly satisfactory for demonstrating these antibodies. Agglutination in dilutions of over 1:300 is considered diagnostic of Weil's Disease (1), and by the end of the third week the titer is frequently over 1:10,000.

Early in the second stage, then, the diagnosis depends upon the recognition of the clinical picture, which in severe cases is characteristic, and upon the identification of the *Leptospira icterohemorrhagiae* in the urine. The technique of this identification must be carefully followed to get results, and is described in detail subsequently. Many failures to establish the diagnosis in this country are probably due to inadequate knowledge of the details essential to the demonstration of the leptospira by this method.

At the end of the second stage the patient begins to show definite improvement in all the manifestations of the disease, and the third stage or stage of convalescence is initiated, usually beginning on the 14th to the 16th day, although its onset may be delayed to the end of the third week of the disease.

*Third stage.* The third stage, or convalescent period of the disease, begins insidiously some time in the latter part of the second week or in the third week of the disease. The temperature is already down, and the icteric index begins to fall. The evidence of renal disease disappears and the patient becomes symptom-free except for rather marked weakness. Usually the hemorrhagic tendency is already gone by the time this stage begins, and the spinal fluid clears rapidly.

In this period, the specific antibodies in the blood reach a very high titer, which is maintained for years. After the third week of the disease, the diagnosis should be established by using the patient's serum to agglutinate and lyse the leptospira. The reaction is highly specific.

Convalescence may be rapid—a week or two—or may last six, eight, or even ten weeks. In some instances the jaundice is very slow to recede, and it may be the last symptom to disappear.

At any time in the third, fourth, or fifth week of the disease, when the patient is symptomatically well, he may have a relapse. Such relapses occur suddenly, and may be accompanied by all of the symptoms which initiated the disease at its onset, or may be quite mild,

(71) and Dragert (72) described two cases of acute vegetative endocarditis in which leptospira were found, parotitis may develop, and may be fatal (30), concomitant disease such as typhoid or paratyphoid (74), and malaria (75), are reported. Terminal purulent meningitis as a fatal complication was reported early by Inada et al (4).

In the non-fatal cases, at about the end of the second week the patient becomes more rational and begins to have a diuresis. This latter symptom usually indicates a favorable prognosis, but according to Lissner (76) may be misleading. The blood urea nitrogen begins to fall, and the jaundice to subside. The general toxicity diminishes, the temperature is already near normal, and the pulse rate begins to fall. At this time, two complications may appear.

The first of these, *iridocyclitis*, was first mentioned by Goebel (77). Strasburger (78) observed it in 44 per cent of cases including mild ones and in the Netherlands the figure is given as 10 per cent and is considered a minimum (1). It may be either unilateral or bilateral, mild, or so severe as to cause blindness. Walch-Sorgdrager (1) could find no cases without recovery.

The second, *optic neuritis*, is apparently less common, and is not of much importance.

Neither complication has been common in the American cases.

During the second stage the blood becomes sterile and the organisms begin to appear in the urine. Most of the evidence (1) indicates that the spirochetes begin to appear in the urine at about the end of the second week. Korthof (80) says he could always find them between the 9th and the 16th days of the disease. There is little accurate information as to the length of time they persist in the urine. Slot and Van den Walle (40) record their presence five months after onset, and Johnson (43) indicates that he observed them after eleven months. The technical difficulties of absolute identification from urine raises some question in these cases. In the Netherlands the general feeling seems to be that they persist for only a few weeks (1).

During the period of leptospiuria, specific antibodies begin to appear in the blood. They can rarely be detected before the 9th or the 10th day, and are usually not of diagnostic titer until the 14th day. By the end of the third week, very high agglutinin and lysin

presenting the classical symptoms of sudden onset, severe headache, high fever, aching muscular pains with calf tenderness, albuminuria, and evidence of urea retention. The onset of jaundice with a declining temperature after five, six, or seven days of illness practically clinches the diagnosis but the final proof must come from finding the causative organism in one way or another.

In the first week of the disease, the *Leptospira icterohemorrhagiae* is circulating in the blood stream and can be demonstrated in the blood by dark field examination or by inoculating a suitable laboratory animal with blood intraperitoneally and reproducing the disease. The former method is the most simple, and should be routinely used.

The technique consists of examining blood under dark field illumination with either the usual high dry lens or the oil immersion lens of the average microscope. The *L. icterohemorrhagiae* appears as an actively motile spirochete. It is from 8 to 15 micra in length and approximately 0.5 micra in width. It is tightly coiled, and when seen usually appears as a series of brightly refractile spots alternately interspersed with non-refractile areas of the same size. This phenomenon is due to the fact that frequently only the surface of the coil nearest the observer is refractile. Careful study will demonstrate the spirochetal nature of the organism. It differs from the well-known *Treponema pallidum* in that it is much more tightly coiled and has a small, sharp hook at each end (occasionally at only one end) which gives the organism the appearance of an "S" or a "C". It has inherent motility in three directions. It moves across the stage, rotates very rapidly on its own axis and also writhes in a whip- or snake-like fashion. The only difficulty one encounters in identifying the organism is the presence of myriads of minute particles of fibrin and other partially precipitated protein normally seen in blood which are in constant motion due to Brownian movement. Careful study will differentiate these artifacts from the typical truly motile, rapidly spinning, spirochete. Fortunately for diagnostic purposes, when the *L. icterohemorrhagiae* is present in the blood, it is usually present in large numbers. Also incubation at 27°C (in the vest pocket) will frequently increase the number of organisms in the specimen and facilitate demonstration.

Blood (5 cc) from a suspected case of Weil's Disease may be injected



with only aching and anorexia. The temperature usually rises to  $102^{\circ}$  or higher during the relapse. Such relapses are usually of only one or two days' duration, but may last a week. A relapse is apparently never of serious consequence (1). Commonly, there is only one relapse, but two or three of diminishing severity are not rare (1). The incidence of relapse appears to be variable in different parts of the world. The figures given run from 28 to 75 per cent (70). They have been very inconspicuous in the American cases, our case No. 4 had one relapse just after leaving the hospital.

In the convalescent period, iridocyclitis may develop if it has not done so earlier. Developing late in the disease, it is usually mild and requires no special therapy except ocular rest. Mild or severe peripheral neuritis may develop (72), it is rarely severe, and proof is lacking that it is due solely to the spirochete and not to vitamin B<sub>1</sub> deficiency. The prognosis in such cases, even though severe at onset, is apparently good (1). Considerable anemia may have developed, and responds slowly to iron therapy.

The most severe complication which may go undiagnosed until late in the disease is leptospiral vegetative endocarditis (72). The number of proved cases is far too small to enable us to draw any helpful conclusions about its symptomatology.

Sub-acute leukemia has been described by Martin and Pettit (51) as a rare complication, but their evidence is not convincing. Probably the picture was similar to the leukocytosis seen in our Case No. 2 in the second week—the white blood count was at leukemic levels, 49,000, and the differential showed many young cells of the granulocyte series, but this cannot be interpreted as leukemia.

Save for an occasional relapse of short duration, the convalescence in Weil's Disease is smooth and uneventful, but frequently quite slow. It is a serious infection, which in severe cases should be followed by a long rest period.

#### DIAGNOSIS

As in typhoid fever, the procedures necessary to establish the diagnosis of Weil's Disease vary, depending upon the duration of symptoms.

A presumptive diagnosis can be readily made in a majority of cases

As in the case of the blood, young guinea pigs must be used 60 to 80 cc of freshly voided, clean urine is centrifuged at 3,000 R P M for 15 minutes and the sediment mixed with 5 to 10 cc of normal, physiological saline solution and injected into the pig intraperitoneally. Certain precautions are necessary to assure good results.

- 1 The urine must have stood not more than an hour before the inoculation is made.

- 2 Strongly acid or strongly alkaline urine quickly destroys the *L. icterohemorrhagiae* and the patient must be given some agent to make his urine approximately neutral when voided.

- 3 The guinea pig must be young (175 grams or less).

This method is satisfactory if the above details are meticulously carried out and provided the peritoneal fluid is examined frequently after the animal develops a fever as described above. Most young animals will become ill, jaundiced, and die, but this is not a necessary prerequisite as many have previously thought.

In the third and subsequent weeks of the disease the *L. icterohemorrhagiae* produces in the host very specific agglutinins and lysins which can be measured (17, 19). These are among the most specific antibody reactions known. In the average case, after three or four weeks the blood serum of the patient will agglutinate a virulent culture of *L. icterohemorrhagiae* in dilutions of 1:10,000 to 1:300,000 and will not agglutinate any other known strains in a titer above 1:250. The lytic reaction occurs at even higher titers. Most observers now agree that agglutination in dilutions of 1:300 or above is diagnostic. The titer is rarely so low, probably never so low in patients who become seriously ill and are jaundiced. This agglutination reaction is useless before the 9th or 10th day of the disease, because no specific antibodies are found. When found in high titer after the 14th day, it is diagnostic. From the 10th to the 14th day, rapidly increasing titer may be used as an accurate diagnostic test.

The specific antibodies remain in the blood for years, perhaps indefinitely, with only moderate fall in titer and the method can be used to prove the pre-existence of the disease in patients with a suspicious past history. Students of the subject agree that strong false positives are non-existent. A negative reaction after the 30th day of illness rules out Weil's Disease. *Note:* Other strains of lepto-

intraperitoneally into a young guinea pig (175 grams or less) After a period of from 10 to 14 days, the pig will become jaundiced and die The organism can then be demonstrated in the liver, the lung, and the kidney of the animal, either by section and staining with the Levaditi or Giemsa stains, or directly by dark field examination of an emulsion of these organs Unfortunately, not all guinea pigs will become ill and die They must be young A modification of the technique described above is said to be more successful After inoculation the animal's temperature is taken daily When a definite daily or sustained temperature rise has taken place, one may aspirate a minute amount of fluid from the peritoneal cavity of the pig, using a glass capillary pipette Dark field examination of this fluid will show a pure culture of the organism and it is not necessary to wait for the onset of jaundice or the death of the animal to establish the diagnosis Exact identification of the strain of spirochete must, of course, be done serologically

For therapeutic reasons, it is most desirable to demonstrate the organism directly in the blood stream in the first week of the disease, because it is during this period that specific therapy is most valuable The other methods should be used as corroborative evidence and as a check on the therapeutic efficacy of any specific agent

In the second week of the disease, the spirochete disappears from the blood stream and begins to be excreted in the urine Also, at the same time, specific agglutinins and lysins appear, but in too small a titer to be of diagnostic value at this stage Also, in the second week of the disease, the spirochete may occasionally be found on direct dark field examination of the cerebro-spinal fluid (91) The organism disappears from the blood stream a little earlier than it does from the spinal fluid, and the concentration of specific antibodies in the cerebro-spinal fluid never becomes as high as it does in the blood

Because not infrequently there are spirochetes of many varieties in normal urine, direct dark field examination of urine is not satisfactory One must depend upon infecting a susceptible laboratory animal with the infected urine This method has proved unsatisfactory in many hands, and is probably one of the very important reasons for failure to establish the diagnosis in this country The difficulty lies in the fact that most physicians and laboratory aides are not cognizant of the details which one must carry out to assure good results

(10 grams daily for three days) during the bacteremic first stage and it did not alter the number of organisms in the blood stream, nor did it in any way influence the course of the disease. Prontosil has been used in the Netherlands without benefit (1).

Soon after the cause of Weil's Disease was established a search for protective antibodies in convalescent patients was begun. The Japanese (4) were the first to demonstrate such antibodies and to use these agents in therapy. By 1916 both horse serum and goat serum containing antibodies against *L. icterohemorrhagiae* had been produced. A little later a curative rabbit serum was developed. None of these sera has been well standardized to date. The most widely used sera come from horses whose blood has been raised to an agglutinating titer of 1:100,000 or higher against *L. icterohemorrhagiae* and *L. canicola* (dog strain). The dose is apparently 60 cc. of such serum (36). Results in Holland (1), England (54), France (52), Germany (50) and particularly Japan (4) indicate that this form of therapy is effective in lowering the mortality rate, especially if given in the first six days of the disease. In Japan (4) for example, the mortality rate in one group of cases was lowered from 30.6 to 18.3 per cent. Much lower figures have since been reported in cases treated early in the disease (1). Data from Amsterdam indicate that relapses are not prevented (86), but that the course of the disease is made much less severe by the use of either convalescent serum or immune horse serum.

Our Case No. 4 was treated with 500 cc. of whole blood from Case No. 2. This blood was given on the ninth day of the disease, at which time the patient had been completely anuric for a period of 30 hours. Within six hours after therapy he began to void and improved steadily thereafter. No antibodies were found in the patient's serum before therapy and they were abundant thereafter. Also spirochetes were readily demonstrable in the blood before therapy and were not found thereafter. This is the first serum-treated case to be reported in this country. Games (101) gave a small amount (30 cc.) of convalescent blood intramuscularly to one patient but complete identification of the injecting spirochete was not made in the recipient.

Walch-Sorgdrager (1) has good evidence to show that while the severity of symptoms and the mortality are favorably affected by the

spira produce jaundice in man, and negative agglutinations against *L icterohemorrhagiae* in suspicious cases should have agglutination reactions with other strains, particularly *L canicola*

In any instance in which one has demonstrated a spirochete in the blood or urine in the first or second week of the disease, agglutination reactions should be used to establish the identity of the organism found, though, so far as is now known in this country, there is little chance that it will be other than *L icterohemorrhagiae*. *L canicola* has been reported only once in a human in this country (17), and is uncommon in Europe where the disease has been vigorously pursued. At least two strains of *L icterohemorrhagiae* exist in this locality.

Complement fixation reactions have been described but are less simple of interpretation, and we recommend the agglutination test as diagnostic. Some experience in handling the method is necessary before it can be done accurately.

#### TREATMENT

Soon after the recognition of *L icterohemorrhagiae* as the etiologic agent in Weil's Disease, many attempts were made to kill the spirochete *in vivo* with specific arsenicals such as salvarsan and neoarsphenamine (16), but without success. Furthermore, there is a real danger in administering such toxic substances in the presence of much liver and kidney disease (32).

Soluble bismuth preparations such as sodium bismuth tartrate given intravenously have been shown to be effective and non-toxic in guinea pigs (33). A few human cases have been treated with soluble and colloidal bismuth compounds with reported success (34). Antimony compounds have proved useless (34).

There is still dispute as to whether the bismuth is bactericidal or bacteriostatic, or whether it merely stimulates the normal body defense mechanism (34, 35).

Because certain soaps and resins are known to dissolve the spirochete *in vitro*, sodium ricinoleate has been used experimentally in animals with some beneficial results, but to our knowledge, no such agents have been used in man.

Our own experience has led us to believe that sulfanilamide is useless. Case No. 1 was treated with large doses of sulfanilamide

(10 grams daily for three days) during the bacteremic first stage, and it did not alter the number of organisms in the blood stream, nor did it in any way influence the course of the disease. Prontosil has been used in the Netherlands without benefit (1).

Soon after the cause of Weil's Disease was established, a search for protective antibodies in convalescent patients was begun. The Japanese (4) were the first to demonstrate such antibodies and to use these agents in therapy. By 1916, both horse serum and goat serum containing antibodies against *L. icterohemorrhagiae* had been produced. A little later, a curative rabbit serum was developed. None of these sera has been well standardized to date. The most widely used sera come from horses whose blood has been raised to an agglutinating titer of 1:100,000 or higher against *L. icterohemorrhagiae* and *L. canicola* (dog strain). The dose is apparently 60 cc of such serum (36). Results in Holland (1), England (54), France (52), Germany (50), and particularly Japan (4), indicate that this form of therapy is effective in lowering the mortality rate, especially if given in the first six days of the disease. In Japan (4), for example, the mortality rate in one group of cases was lowered from 30.6 to 18.3 per cent. Much lower figures have since been reported in cases treated early in the disease (1). Data from Amsterdam indicate that relapses are not prevented (86), but that the course of the disease is made much less severe by the use of either convalescent serum or immune horse serum.

Our Case No. 4 was treated with 500 cc of whole blood from Case No. 2. This blood was given on the ninth day of the disease, at which time the patient had been completely anuric for a period of 30 hours. Within six hours after therapy he began to void, and improved steadily thereafter. No antibodies were found in the patient's serum before therapy and they were abundant thereafter. Also, spirochetes were readily demonstrable in the blood before therapy and were not found thereafter. This is the first serum-treated case to be reported in this country. Gaines (101) gave a small amount (30 cc) of convalescent blood intramuscularly to one patient but complete identification of the infecting spirochete was not made in the recipient.

Walch-Sorgdrager (1) has good evidence to show that while the severity of symptoms and the mortality are favorably affected by the

use of immune serum, the duration of the febrile period is not altered, and also, even when used early, it is not always effective (20). However, as regards this latter statement, we feel that evidence has not yet been produced to indicate that adequate dosage was used in these cases.

There is some evidence (1) to indicate that in serum-treated cases the antibody titer of the patient does not reach as high levels as in the untreated cases, but apparently in either circumstance adequate immunity lasts at least ten years (73), and probably longer.

Serum prophylaxis has been effectively used in animals (36, 4), and has been tried in human beings (100). The known incidence of the disease in areas where it has been adequately studied indicates that mass prophylaxis is not necessary in man except in certain isolated occupations, especially fish cleaners and certain types of sewer workers. More careful and detailed study of the foci of infection will probably result in elimination of these foci rather than mass immunization for the population.

In a word, then, the treatment of choice is immune serum. As yet, the American drug houses have done nothing about preparing such sera, nor can they be expected to do so until City and State laboratories make available the necessary diagnostic procedures, and until the true incidence of the disease in the United States becomes known.

Careful supportive therapy, aimed at good nutrition, proper water and acid-base balance control, good circulation, and adequate isolation, are of course indicated. Until immune sera appear on the American market, convalescent serum or whole blood transfusions should be used when possible.

#### PROGNOSIS

The prognosis is dependent upon the following factors:

- 1 Age of the patient
- 2 The presence or absence of jaundice
- 3 The degree of renal failure
- 4 The function of the heart
- 5 The extent of the hemorrhagic diathesis

Well's Disease is practically unknown in infants, and is rare in children. The mortality rate increases rapidly with advancing age,

and is most significant in patients over 60 years of age The following table is from Walch-Sorgdrager

	DEED	FATALITY RATE
		<i>per cent.</i>
Out of 11 persons aged 1 to 10	0	0
Out of 210 persons aged 10 to 40	15	7.1
Out of 49 persons aged 40 to 60	12	24.0
Out of 15 persons aged 60 or over	9	60.0
Out of 85 persons of unknown age	8	9.4
370	44	11.9

This series came from Holland Of the 370 cases, approximately 50 per cent were jaundiced The number of serum-treated cases is not stated

There is an old axiom, now well known in Europe, which states that in Weil's Disease where there is no jaundice, there is no mortality (19) We have been able to find in the world literature a report of only one case in which death occurred without jaundice (1) The intensity of the jaundice when present is probably not nearly so significant as the patient's age, although icteric indices of over 200 should always be looked upon gravely

The degree of renal failure as indicated by the urine output, and the degree of urea retention, are important for prognosis Oliguria and a high blood urea are usually serious, and anuria is always a grave sign A high blood urea without oliguria is usually not a serious sign The amount of albumin and casts in the urine are of little help in deciding the outcome

In most cases, the cardio-vascular system responds well to the disease, but occasionally a very rapid pulse, out of proportion to the temperature and associated with relatively low blood pressure, is encountered, and should warn the physician that his patient is in danger In older people, mild congestive failure will frequently respond to the usual therapy and is not important unless associated with persistently low blood pressure Pronounced and long-continued bradycardia is of serious significance

Usually the hemorrhagic diathesis is not of significance, but rarely, in the very ill, older individuals, bleeding from the respiratory, gastro-



use of immune serum, the duration of the febrile period is not altered, and also, even when used early, it is not always effective (20). However, as regards this latter statement, we feel that evidence has not yet been produced to indicate that adequate dosage was used in these cases.

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onset of the jaundice—three to nine days after the beginning of severe symptoms—should lead one to search for the etiologic spirochete

In the most severe cases in some parts of the world the chief differential diagnostic problem is presented by yellow fever. In this country the problem should rarely arise. The characteristic intense facial flush and very red lips of yellow fever are not present in Weil's Disease. Yellow fever is usually preceded by a shaking chill followed by a rise in temperature. At this time the pulse is fast and the face markedly flushed. The face shows anxiety instead of lethargy.

If yellow fever is not fatal within 48 hours the temperature characteristically falls on the third day to rise again in a day or two. In Weil's Disease if there is much fever it usually remains well up until after the jaundice begins. In the jaundiced period relative bradycardia is the rule in yellow fever and tachycardia the rule in Weil's Disease. In yellow fever the absence of leukocytosis and a high hemoglobin content are considered pathognomonic signs. Quite the reverse is true in Weil's Disease.

A careful study of the patient's blood in the first ten days of the disease will make the diagnosis of Weil's Disease apparent when all other signs are confusing. •

Typhoid fever and malaria have been reported as existing coincidentally with Weil's Disease (82). The former is the more likely since the two causative organisms have a similar habitat (i.e., dirty water). Since the incubation period for typhoid fever is considerably longer than for Weil's Disease typhoid will make its appearance when Weil's Disease is at its peak. The development of a sustained unexplained high fever at this stage should demand repeated blood cultures in a search for *B. typhosus*.

#### THE MECHANISM OF JAUNDICE

In a recent review of the literature on the liver and biliary tract, Greene and Farrell (58) concluded that the pathogenesis of the icterus in Weil's Disease is as yet obscure.

Clinical observations show that it is not due solely to large biliary tract obstruction as severe jaundice may occur without acholic stools. In fact even with the most intense jaundice (icteric indices over 300) acholic stools are rare.

intestinal, and urinary tracts may become so serious as to become a definite hazard to life

A sustained high or rising temperature, persisting after the second stage has been well established, is always serious. A low or even normal temperature is of no prognostic significance.

In Japan, it has been definitely shown that early diagnosis and therapy can materially lower the mortality rate in all age groups.

#### DIFFERENTIAL DIAGNOSIS

Early in the disease, before the onset of jaundice, the clinical picture of Weil's Disease suggests almost any severe infection associated with bacteremia. Typhoid fever is commonly diagnosed because in Weil's cases the pulse may be relatively slow for the fever. The absence of rose spots, the negative blood culture, the marked calf tenderness, if present, and cells in the spinal fluid, will usually rule out typhoid. The incubation period of typhoid is usually about two weeks, and for Weil's Disease it is nine days.

In mild cases in which no jaundice develops, many cases have gone, and will go, undiagnosed as anything but "la Grippe." The chief aid seems to us to be that in influenza-like states the patient promptly feels better when the temperature drops, in Weil's Disease the patient frequently feels quite badly for several days after the temperature becomes normal. Vomiting is much worse and much more frequent than in "influenza," and a careful study of the urine and blood may show minimal evidence of renal and hepatic disease which would otherwise be overlooked.

When jaundice is present in mild cases, the most important diagnostic problem is to differentiate Weil's Disease from acute catarrhal jaundice. This differentiation should not be difficult because in the latter the white blood count is relatively low and lymphadenopathy and a palpable spleen are the rule. The reverse is true with Weil's Disease. Evidence of renal disease, meningeal involvement, and a hemorrhagic tendency are absent in catarrhal jaundice. The dull, heavy feeling in the region of the duodenum, which may result in vomiting when pressure is applied to the epigastrium in catarrhal jaundice, is not common in Weil's Disease. In the latter, if there be abdominal disorder, it is real pain. In Weil's Disease, the time of

hemorrhagic tendency is severe, the jaundice may be too massive to be explained on this basis and frequently gives Van den Bergh reactions indicating its hepatogenous origin

From the available material we are forced to conclude that the mechanism of icterus in Weil's Disease is not entirely established. It is probably due in large part to true hepatitis but it may also be contributed to by hemolysis and by intrahepatic biliary tract obstruction. Our own autopsied cases indicate severe degenerative and inflammatory change throughout the liver parenchyma as the most significant lesion.

#### THE NATURE OF RENAL FAILURE

Evidence of renal disorder is one of the outstanding features of the disease. The urine early shows albumin and in more severe cases frequently shows red cells, casts, and white cells. Oliguria is a common phenomenon and anuria is not infrequently a cause of death. Urea retention begins early in the disease, and may be severe, the blood urea nitrogen reaching levels of 150 mgm % or higher. When severe it is frequently associated with acidosis, again of renal origin.

The kidneys at autopsy are always firm and swollen (60). Subcapsular and interstitial hemorrhages may be found (60). There is necrosis of the tubular epithelium especially of the convoluted tubules (60). Frank hemorrhagic nephritis with much hemorrhage into Bowman's capsule has been described (60). This nephritis is usually very acute but may also show a good deal of early interstitial fibrosis. Interstitial cellular infiltration with large numbers of lymphocytes and some polymorphonuclear leukocytes is commonly described (66). Jeghers (5) feels that the tubular damage is usually much more apparent than is the glomerular damage and concludes that the extent of the renal damage is often better indicated by the clinical and laboratory findings than by the histologic structure of the kidneys.

It is generally conceded that the renal damage, chiefly tubular, is toxic in origin and due to the spirochete rather than to bile. This point however is by no means proved. In our own cases the extent and nature of the tubular damage appeared to be of itself sufficient to account for the renal failure. The mechanism would not be dissimilar to that seen in mercuric poisoning.

The morbid anatomy shows considerable hepatic cell degeneration, granulation of the liver cells with vacuolation, pycnosis, and karyolysis have been demonstrated (59, 60), and cells with two nuclei and mitotic figures have been described by McNee (60). One of our own cases showed considerable central hepatic necrosis. It is apparent that the mechanism of the jaundice may in part be due to hepatitis itself.

Stokes, Ryle, and Tytler (61) demonstrated marked inflammation of the smallest biliary ducts and concluded that the jaundice was due to obstruction in these passages. Dawson and Hume (62) showed that in some instances there was no pathological evidence of biliary tract obstruction. Kaneko (63) concluded that it was due to intra-acinous biliary obstruction without actual blockage of the bile channels, but subsequently changed his mind as other work showed evidence of dilatation and rupture of bile capillaries with escape of bile into the general circulation (64). Busch (65), studying the liver physiology in infected guinea pigs, believed that the jaundice was due to extensive blood destruction with retention of bilirubin resulting from functional impairment of the liver, the latter due to edema of that organ. This work was based in part on the indirect Van den Bergh reaction, but Oka (64) has shown the reaction to be direct in human beings. Collected European cases show that any of the known Van den Bergh reactions may take place (1), and that they are not predictable from a clinical study of any given case.

The duodenitis theory with partial obstruction at the ampulla of Vater (62) is no longer held by even the original authors.

Many authors have felt that the icterus was due to increased hemolysis, and point to the evidence of increased blood destruction in the spleen as well as to the clinical evidence of anemia. This theory is not tenable in the vast majority of severe cases because the jaundice is out of all proportion to the demonstrable blood destruction.

Our own tests have shown an actual decrease in red cell fragility, and Case No. 2, with an icteric index of 300, showed no appreciable fall in red count. Bone marrow studies showed no evidence of hypertrophy and hyperplasia in the erythropoietic system.

The jaundice cannot be explained as a direct result of hemorrhage into the tissues with subsequent bilirubin formation. Even when the

in the calves has in Weil's Disease a pathological basis which is one of the primary distinguishing features of the disease. According to Jeghers (5), the lesion is most frequently found in the calf. Most other muscles are similarly, but less extensively, affected. The gross appearance is usually normal (68) or may show minute hemorrhages or bile-stained foci of degeneration as large as 5 mm in diameter (5).

Microscopically, the process characteristically selects isolated fibers and only part of a fiber. "There is vacuolation, swelling, loss of striation, hyalinization, infiltration with histiocytes, plasma cells, and polymorphonuclear leukocytes, breaking up of the fibers into large, round lumps of hyalin material, resorption and proliferation of the nuclei of the sarcolemma. Hemorrhage into the empty sheath has been described" [Jeghers (5)]. The picture differs considerably from the Zenker's degeneration seen in typhoid fever, both in distribution and appearance.

#### MORBID ANATOMY

At autopsy, most cases of Weil's Disease reveal generalized jaundice and lesions involving the following structures:

- 1 Kidneys
- 2 Liver
- 3 Capillaries
- 4 Skeletal muscles

1 The kidneys, unless previously damaged, are usually enlarged. They usually show:

- (a) The greenish-brown stain of jaundice,
- (b) Swelling and more or less marked necrosis of the epithelium of the convoluted tubules, and
- (c) Interstitial infiltration of lymphocytes, and, to a lesser degree, polymorphonuclear leukocytes and eosinophiles (66).

Small hemorrhages may be seen under the capsule, into the interstitial tissue, or into the tubules (60). Granular, bile-stained casts in the lumen of the tubules along with inflammatory cells and cellular debris are common (5). The glomeruli are usually undamaged, but changes in Bowman's capsule and the glomerular tuft

In Weil's Disease we are confronted with an *hepatorenal syndrome*. In some instances the renal damage appears far more prominent than the hepatic, and in others the reverse appears to be true. Mild urea retention and slight oliguria with severe jaundice is fairly common—Case No 3. Severe urea retention and anuria with only slight jaundice has been described (1). We feel that the evidence warrants the working hypothesis that both renal and hepatic disease, though one may markedly influence the other, are probably both due in some way to the infecting spirochete. The exact pathogenesis of the renal and hepatic disorders is as yet unknown.

#### THE HEMORRHAGIC TENDENCY

The hemorrhagic tendency is quite variable. In the early Japanese writings it was so pronounced as to provoke the term *icterohemorrhagica*. In many cases in Europe, even with icterus, evidence of hemorrhage has been absent (1). Review of the literature shows that early in the disease nasal hemorrhage is most common. Later, cutaneous and mucous membrane hemorrhages occur. They have been described in the conjunctivae. Occult blood may appear in the stool, and variable amounts of blood have been described in the urine. Herpes, when present, is usually hemorrhagic. Lung hemorrhage with a hemorrhagic pneumonia was seen in two of our cases.

Pathologically, the hemorrhagic diathesis appears to be due to primary capillary damage (5, 60, 1), and not to any disorder of the blood and its clotting mechanism. We have demonstrated decreased red cell fragility and normal bleeding and clotting times, as well as normal platelet counts and prothrombin time. Small hemorrhages have been described in nearly every organ in the body, but are most commonly found in the striated muscle, kidney, adrenal, liver, stomach, spleen, and lung. They are rare in the brain but may involve its substance (67) or only its coverings (61). Jeghers (5) describes them in pancreas, pleura, peritoneum, pericardium, endocardium, and bladder, as well as the usual sites. Very rarely, death may result from massive gastro-intestinal hemorrhage (68).

#### MUSCULAR ACHING AND TENDERNESS

Unlike most acute infectious processes, the severe muscular aching associated with tenderness of the muscles especially over the back and

in the calves has in Weil's Disease a pathological basis which is one of the primary distinguishing features of the disease. According to Jeghers (5), the lesion is most frequently found in the calf. Most other muscles are similarly, but less extensively affected. The gross appearance is usually normal (68) or may show minute hemorrhages or bile-stained foci of degeneration as large as 5 mm in diameter (5).

Microscopically the process characteristically selects isolated fibers and only part of a fiber. "There is vacuolation, swelling, loss of striation, hyalinization, infiltration with histiocytes, plasma cells, and polymorphonuclear leukocytes, breaking up of the fibers into large round lumps of hyalin material, resorption and proliferation of the nuclei of the sarcolemma. Hemorrhage into the empty sheath has been described" [Jeghers (5)]. The picture differs considerably from the Zenker's degeneration seen in typhoid fever, both in distribution and appearance.

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may be impossible to differentiate from those of acute glomerulonephritis (81) Interstitial infiltration with polymorphonuclear leukocytes almost to the extent of abscess formation has been described (68)

The renal damage is predominantly tubular All of the stages of degeneration, from cloudy swelling to actual necrosis, may be found Certainly the profound swelling of the tubular epithelium and the collections of cellular debris within the lumina must play an important role in the impairment of renal function The picture in the kidney is analogous in some respects to that found in bichloride of mercury poisoning Pick (68) believes this damage to be toxic in origin, due to the spirochete and not to the bile Proof of this point is lacking Within the interstitial tissues, and more particularly in the lumen of the tubules (especially the proximal, convoluted loops), the spirochetes are readily found In our hands the Levaditi silver impregnation technique has been most satisfactory in demonstrating them The staining process shortens and thickens the organism, but its morphology is otherwise unaltered and appears as a black coil in either the "S" or the "C" form Careful study makes them easily differentiable from artifacts

2 The liver may appear normal in the gross, but it is usually slightly enlarged and bile-stained It is never shrunken as in acute yellow atrophy (5) Extra hepatic bile duct obstruction is absent There has been much dispute concerning intra-hepatic biliary obstruction Certainly there is no evidence of obstruction in any of the medium and large ducts, and in most cases evidence of obstruction even in the bile capillaries is absent Stokes (61) has described inflammation and obstruction of the smallest of the biliary ducts Dawson and Hume (62) were unable to corroborate this finding Kaneko (63) could find no actual blockage of even the smallest bile ducts, but thought that he could demonstrate intra-acinous biliary obstruction Oka (64) describes dilatation and rupture of some of the smallest bile capillaries with spilling of bile directly into the blood stream One report (83) describes mucus plugs in the common duct, but this must be exceedingly rare

Microscopically, three lesions are commonly reported (a) There is a proliferation of hepatic cells Much of the hepatic cell division may be amitotic (84), but mitotic figures and cells with two nuclei

are not uncommonly seen (60) We were impressed by the absence of any indication of such reparative activity The regenerative ability of the liver is well known and it is not unusual to find bi-nucleated liver cells and even mitotic figures in cases of hepatic injury and occasionally in relatively normal livers, so that we do not feel that proliferation of the liver cells is a particularly distinctive feature of Weil's Disease pathology (b) Evidence of degeneration and inflammation are seen Some of the liver cells show swollen nuclei and cloudy swelling Vacuolation of the cell with pyknosis and karyolysis of the nuclei have been described (59) Loosening or dissociation of the cells as though pushed out of their normal position by widening of the perisinusoidal lymph spaces perhaps by edema is described by Valassopoulos (14) Fatty infiltration is absent or slight (5) Varying degrees of necrosis usually slight and focal are seen and this may occasionally be so extensive as to simulate yellow atrophy (the liver however is not diminished in size) In our cases No 5 and No 6 central zone necrosis with rarefaction and dissociation of the cells was the predominant picture (c) Evidence of biliary stasis in the central part of the lobule is commonly found (5) It may appear as small droplets or granules in the central bile capillaries or in the cytoplasm of swollen cells There is none in the periphery of the lobule (5)

Other changes occasionally seen are deposition of fat in small droplets in the Kupffer cells and infiltration of the portal spaces by lymphocytes and a few polymorphonuclear leukocytes and eosinophiles Minute hemorrhages in the portal spaces and beneath the capsule are occasionally seen Rarely, scattered hemorrhages throughout the liver may be quite prominent

Spirochetes may be found in the liver usually in the perisinusoidal lymph spaces but they are more difficult to demonstrate than in the kidneys We were able to demonstrate a rare organism in the liver of case No 5

Jeghers (5) believes the changes are simply the result of an unusually severe infection In our experience the liver lesions differ from the usual toxic hepatosis considerably but this may not be true in a larger group of material The lesion certainly is not as characteristic as that found in yellow fever

3 The damage to capillaries is manifested by minute hemorrhages

generally distributed throughout the body, which may be so slight as to go unnoticed without careful search, or which may be profound. They are most common under the peritoneum and pleura and in the gastro-enteric tract, kidneys, nasal mucosa, adrenals, and skin (5). They have been described beneath the endocardium and pericardium, under the capsule of the liver and in its portal spaces, in the mesentery, spleen, pancreas, and bladder.

Hemorrhage in the trachea, bronchi, and lungs, may be minute and widely scattered, or may be larger and confluent with other cellular infiltration producing the picture of hemorrhagic pneumonia.

Hemorrhages in the brain and meninges were described by Miller (67), who also found minute hemorrhages in the tibial nerve. Other peripheral nerves have been found to be involved (1).

In the severer cases the hemorrhage takes a prominent place and is responsible for the epistaxis, hemoptysis, hematemesis, hematuria, and melena occasionally seen. One case is said to have died of gastro-intestinal hemorrhage (68).

The skin lesion may be only scattered petechial hemorrhage, or may be extensive purpura and ecchymosis. Detailed studies of the pathology of the skin lesions are too few to permit a detailed description of the exact source of the bleeding.

Hemorrhages into the adrenals are common and may be massive and very destructive (87), but we are unable to find a clinical description suggestive of an adrenal death. The pituitary, thyroid, parathyroids, and gonads, have not been extensively studied, but do not appear to be seriously damaged. Minute hemorrhages in these glands are not unusual.

4. The skeletal muscles show a characteristic lesion most readily demonstrable in the calf. Other muscles, such as the pectorals, deltoids, and the muscles of the back, are affected similarly but less extensively. The gross appearance may be normal (68), or there may be punctate hemorrhages or bile-stained foci of degeneration measuring several millimeters in diameter (5).

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substance of the fibers into larger round lumps of hyalin material, and reabsorption and proliferation of the nuclei of the sarcolemma. Hemorrhage into the empty sheath has been observed [Jeghers (5)] We have not had the opportunity to observe this lesion. According to Jeghers it differs markedly from Zenker's degeneration seen in typhoid fever. These authors believe the lesion is one of the most characteristic lesions of the disease. Spirochetes are rarely found in this lesion.

Other pathological changes are occasionally seen but are by no means as constant as the four prominent findings described above.

The lungs may be normal or may show hemorrhagic pneumonia. The pleura may be dotted with hemorrhages (68). Confluent lung hemorrhages resembling infarctions are described by Hart (88).

The heart may be normal but may show some damage. Cellular infiltration around the vessels and in the myocardium is seen (66). Myocardial degeneration similar to that in skeletal muscle has been described (89). Inflammation of the endocardium and pericardium (67) sometimes occurs and Dräger (72) has described two cases of vegetative endocarditis in which he was able to demonstrate the spirochetes in the vegetation. In one of our cases we suspected such a lesion but were unable to demonstrate the organism.

The spleen is usually not enlarged (5, 1) and is firm. Hemorrhages and deposits of hemosiderin are occasionally seen.

The gastric mucosa is commonly studded with petechial hemorrhages. Catarrhal inflammation of the duodenum and terminal ileum may be present (87). Dräger (72) described one case showing colitis with hemorrhage and necrosis in the large bowel. Whether these lesions are due to primary capillary damage due to the organism or are the result of icterus or uremia is not known.

The pancreas is not remarkable except for occasional small hemorrhages (87).

The lymph nodes are usually not enlarged. In cases in which the infection took place through the abraded skin the local nodes may show acute inflammation (90).

Spirochetes are distributed in every part of the body (1). They are most readily demonstrable in the kidneys and liver. Jeghers (5) gives the following in the order of the frequency with which they are

generally distributed throughout the body, which may be so slight as to go unnoticed without careful search, or which may be profound. They are most common under the peritoneum and pleura and in the gastro-enteric tract, kidneys, nasal mucosa, adrenals, and skin (5). They have been described beneath the endocardium and pericardium, under the capsule of the liver and in its portal spaces, in the mesentery, spleen, pancreas, and bladder.

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the spinal fluid (1) The agglutinin-lysis test rarely gives a positive result in dilutions of over 1:100 which is not diagnostic but the blood of such patients has a diagnostic agglutination titer after the third week of the disease

No cases of pure spirochetel meningitis have been reported in this country From a perusal of the literature it seems to us likely that a careful study of the renal and hepatic functions of such patients will probably lower the incidence of pure meningitis very considerably

#### OTHER ACUTE SPIROCHETAL INFECTIONS

The Dutch at Amsterdam under Professor Schuffner have studied pathogenic spirochetes the world over and have identified at least a dozen serologically distinct strains any one of which may produce disease in man Most of these come from the tropics and from relatively poorly civilized parts of the world To date the only one of significance to us in the United States other than *Leptospira icterohemorrhagiae*, is *Leptospira canicola* which produces a Weil's-like disease in dogs (Note dogs are susceptible to true Weil's Disease)

This disease is transmissible to man One such case has been reported in this country (17) In the Netherlands searching for it carefully the Institute of Tropical Hygiene was able to find only 12 human cases in a series of more than three hundred and fifty Weil's Disease cases Most of their cases were not seriously ill and were not jaundiced Meyer's case (55) in this country had jaundice Apparently large epidemics may occur in dogs without any appreciable number of transmissions to man The diagnostic methods for both dog and man are identical with those of Weil's Disease

The usual terminology given for this disorder in both dog and man, is Canicola Fever\*

Too few cases have been carefully studied to draw any conclusions as to mortality or therapy

#### CASE REPORTS

The following is a report of seven cases of Weil's Disease seen at this hospital within the past year Of the seven all were jaundiced Five recovered and two died The autopsy findings of the two

\* Not in American Medical Dictionaries

found Kidney, liver, adrenals, myocardium, intestinal wall, appendix pancreas, prostate, lung, spleen, lymph nodes, skeletal muscle, and the wall of the bladder [some of the data derived from Kaneko (63)] We were unable to demonstrate them in any organs save in the kidney and liver It must be extremely difficult to demonstrate them in the brain

We have made no effort to cover all of the very rare isolated pathological findings, because they can be only corroborative evidence, and proof that they are due to the spirochete of Weil's Disease is frequently lacking

#### MENINGITIS LEPTOSPIROSA (1)

The meningitis usually associated with Weil's Disease is mild and insignificant, except as it aids in differentiating the disease from some of the other causes of jaundice

The incidence of meningitis in Weil's Disease is unknown because lumbar puncture has not been done in most instances unless the patient had clinical evidence of meningeal involvement We feel that routine punctures are indicated and will show a high incidence of mild meningeal involvement

The French have been able to demonstrate what they call "Spirochètose Meningée pure" (91-94), meningitis due to the *Leptospira icterohemorrhagiae*, without any of the other clinical evidence of Weil's Disease Their work has been adequately confirmed in the Netherlands (1) *Leptospira canicola* also produces pure spirochetal meningitis occasionally (1)

The symptoms and signs vary widely in severity, but differ not at all from those of other mild and severe meningitides The spinal fluid is usually under increased pressure and the Pandy reaction is weakly positive It may be negative (our case No 4) The cell count may be anything from 10 to 3,000, but usually does not go above 200 or 300 The cytology may show from 30 to 90 per cent polymorphonuclear leukocytes, the remainder are lymphocytes, but usually shows about 50 per cent of each It reaches its peak about the 15th day of the disease, and subsides thereafter The sugar and chlorides are usually normal and the Wassermann reaction negative The gold-sol curve has not been extensively studied

Early in the disease the organisms are said to be demonstrable in

were dirty, the tongue heavily coated and the throat quite red. The pillars of the throat and the posterior pharyngeal wall were covered with a yellowish-grey exudate which could be scraped off easily without producing bleeding. The remainder of the physical examination was at that time negative.

Admission laboratory work at that time revealed: RBC, 5 05 M.; Hgb, 14.5 gms.; WBC, 18,900 (92 per cent polymorphonuclears, many young forms).

The urine was normal except for a large amount of albumin. There were no cells or casts. Blood Wassermann, negative. An X-ray of the chest showed evidence of early infiltration in the left lower lobe. Bacteriological study of the throat exudate showed no hemolytic streptococci and no virulent diphtheria organisms.

On the second hospital day, the patient's temperature dropped to normal and he became definitely icteric. The leukocytes rose to 20,000, 96 per cent polymorphonuclears. On the third day he was stuporous, had an icteric index of 120 and his blood gave a positive direct Van den Berg reaction. The temperature slowly rose to 102° on the fifth hospital day, the jaundice increased (icteric index 240), blood urea nitrogen rose to 81 mgm. per cent, the urine remained unchanged except for the presence of large amounts of bile, and the stools showed evidence of complete biliary obstruction. At this time he was seen by a medical consultant and transferred to the Medical Service for further study.

Physical examination at the time of admission to the Medical Service revealed: Temperature, 102°F; Pulse, 110; Respiration, 60; B.P., 120/70.

The patient was very seriously ill, disoriented, and had Cheyne-Stokes respiration. The skin was deeply stained with a greenish-yellow jaundice. The throat showed marked erythema and there were still a few patches of exudate present. The neck was not stiff, and no lymphadenopathy was apparent. The heart and lungs were normal. The abdomen was markedly distended, the stomach dilated and the liver appeared to be enlarged to percussion but no edge could be felt. There was tenderness of the calf muscles, and all deep tendon reflexes were diminished.

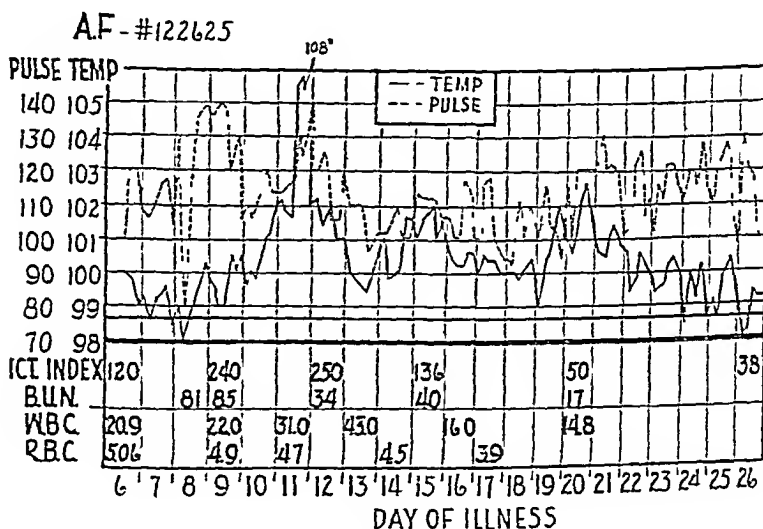
The laboratory findings at that time showed a leukocytosis of 22,000, 80 per cent polymorphonuclears, 20 per cent lymphocytes, and many young forms in the granulocyte series. The urine showed a ++ albumin, a few red cells and white cells, and much bile. The stools were completely clay colored and gave no positive test for bile. The icteric index was 240 and the blood urea nitrogen was 85 mgm. per cent. The blood serology was negative. Lumbar puncture was not done.



fatal cases, No 5 and No 6, are discussed together, after the clinical reports. In the non-fatal cases, the diagnosis was proved by specific agglutinations, and in the fatal cases by demonstrating the organism in the tissues.

*Case No 1* A F (#122625), a white male, aged 26, unemployed, was admitted to the Contagious Division of the Cincinnati General Hospital on June 11, 1939, complaining of severe sore throat of four days' duration.

Five days before admission to this hospital, the patient was swimming in the Ohio River. He had done this several times in the previous week.



#### CASE 1

Four days before admission, he very abruptly developed a severe frontal headache associated with some fever and marked malaise, but no chill. In the afternoon of the same day he developed a severe sore throat and experienced considerable difficulty in swallowing. He became very lethargic, had profound anorexia and marked prostration.

On physical examination, the vital signs were as follows: Temperature, 100°F, Pulse, 102, Respiration, 25, B P, 130/70.

This well-developed and well-nourished Italian male was first admitted to the Contagious Division of the Cincinnati General Hospital on June 11, 1939, at which time he was acutely and seriously ill, semi-stuporous, and hiccoughing frequently. His sclerae are described as "muddy," his teeth

were dirty, the tongue heavily coated, and the throat quite red. The pillars of the throat and the posterior pharyngeal wall were covered with a yellowish-grey exudate which could be scraped off easily without producing bleeding. The remainder of the physical examination was at that time negative.

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The urine was normal except for a large amount of albumin. There were no cells or casts. Blood Wassermann, negative. An X-ray of the chest showed evidence of early infiltration in the left lower lobe. Bacteriological study of the throat exudate showed no hemolytic streptococci and no virulent diphtheria organisms.

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Physical examination at the time of admission to the Medical Service revealed Temperature, 102°F, Pulse, 110, Respiration, 60, B P, 120/70.

The patient was very seriously ill, disoriented, and had Cheyne-Stokes respiration. The skin was deeply stained with a greenish-yellow jaundice. The throat showed marked erythema and there were still a few patches of exudate present. The neck was not stiff, and no lymphadenopathy was apparent. The heart and lungs were normal. The abdomen was markedly distended, the stomach dilated, and the liver appeared to be enlarged to percussion but no edge could be felt. There was tenderness of the calf muscles, and all deep tendon reflexes were diminished.

The laboratory findings at that time showed a leukocytosis of 22,000, 80 per cent polymorphonuclears, 20 per cent lymphocytes, and many young forms in the granulocyte series. The urine showed a ++ albumin, a few red cells and white cells, and much bile. The stools were completely clay colored, and gave no positive test for bile. The icteric index was 240 and the blood urea nitrogen was 85 mgm per cent. The blood serology was negative. Lumbar puncture was not done.

That evening he had a severe chill and his temperature rose to 108°. He lapsed into deep coma and oliguria became pronounced. Ice packs lowered the temperature to 102°, after which the patient was delirious.

He was given sulfanilamide, 500 cc of a 1 per cent solution in saline, twice daily for three days beginning the third day in the hospital (two days on the Contagious Division, and one on Medicine). At that time motile spirochetes<sup>3</sup> were demonstrated in the blood and continued to be found daily throughout the period of sulfanilamide therapy. They did not disappear from the blood until three days after the drug had been discontinued (the twelfth day of the disease, the eighth day in the hospital).

In the next 15 days his temperature gradually fell to normal, but a marked tachycardia—100 to 130—persisted. During this time his white count rose to 43,000, and then subsided rapidly to 15,000. The urine remained unchanged. The stools began to show bile in increasing amounts on the twelfth hospital day. The icteric index reached a peak of 240 on the sixteenth hospital day, at which time the temperature was 99.5°F, and the blood urea had already fallen to 13 mgm per cent. He remained lethargic with occasional bouts of delirium, and was dangerously ill until about the 20th hospital day, at which time it became apparent that he would live.

From that time on he was essentially afebrile. The icteric index returned to normal on the 40th hospital day. The stools became normal and all evidence of renal disease disappeared.

Serum taken on the 30th day of the disease (34th hospital day) showed a strongly positive agglutination titer against *Leptospira icterohemorrhagiae*, of 1:10,000.

He had no relapses, and was discharged well except for moderate tachycardia—100 to 110—on his 42nd hospital day. On examination one month later, he was found to have gained weight, was employed, and no evidence of residual disease could be found.

*Case No 2* F E (#123728), a colored male laborer, aged 32, was admitted to the Cincinnati General Hospital on July 5, 1939, complaining of pain in the chest of four days' duration.

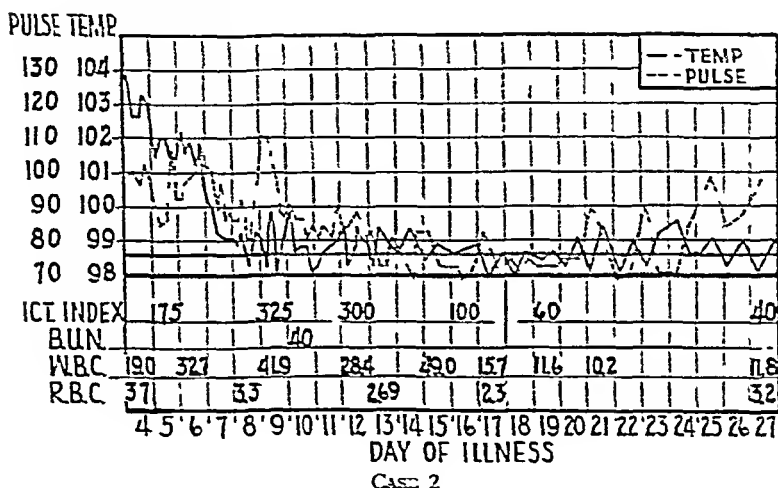
Three days prior to admission, this man suddenly developed a severe shaking chill, followed immediately by right upper quadrant pain which was exaggerated by respiration. The following day he had a lesser chill and developed a cough productive of sputum, at first bloody, and later brown in

<sup>3</sup> First demonstrated by Doctor Robert Kingsland, Junior Assistant Resident in Medicine, Cincinnati General Hospital.

color. He believed that he had had a high fever since the onset. For a few days prior to the onset he had had a slight head cold. There were no other symptoms and he was unaware of the presence of jaundice. Up to the time of admission he was employed as a cook in one of the local fish houses.

This well-developed and well-nourished colored man was admitted to the Medical Service of the Cincinnati General Hospital on July 5, 1939, complaining bitterly of right thoracic and upper abdominal pain. The vital signs were as follows: Temperature, 103.4, Pulse, 104, Respiration 30, B.P. 120/80.

FE.-#123728



He appeared acutely and seriously ill. The skin and sclerae were markedly icteric and there was a mild catarrhal palpebral conjunctivitis. There was moderate nuchal rigidity and tenderness on pressure over the sixth and seventh cervical vertebrae. The movement of the right chest was markedly restricted and respiration was rapid and shallow. There was an occasional inspiratory grunt. There was marked hyperaesthesia over the entire lower half of the right chest. Percussion revealed some dullness over the right lower lobe and in this area the breath sounds were of diminished intensity. A few moist rales could be heard. There was no tubular breathing, nor increase in fremitus over this area. The right diaphragm moved poorly. The remainder of the examination of the lungs

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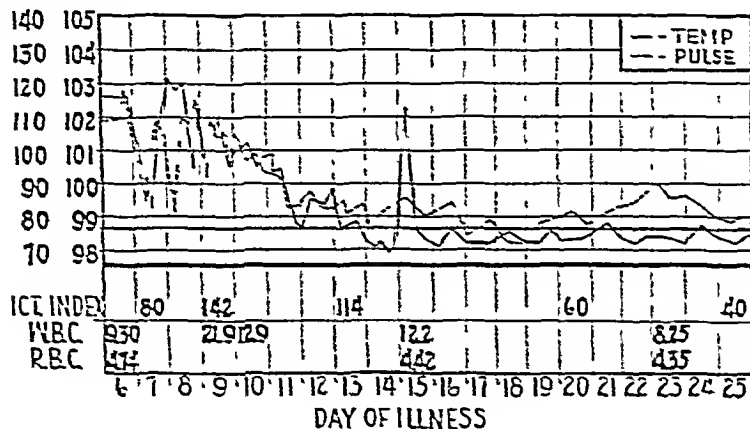
<sup>3</sup> First demonstrated by Doctor Robert Kingsland, Junior Assistant Resident in Medicine, Cincinnati General Hospital.

*spira icterohaemorrhagiae* were positive in dilutions up to 1:30 000 in the third week of the disease.

During the first four days in the hospital the patient ran a very stormy course with delirium severe chest pain and rapidly increasing icterus. At no time were the physical findings in the chest as marked as one might have expected from the X-ray examinations. After the fourth hospital day, the temperature returned quickly to normal but at the same time the icteric index rose to 325 and the white blood count rose to 50 000. In spite of a normal temperature and normal pulse rate, he remained stuporous, occasionally delirious, and it was not evident that he was going to recover

JM - #123582

PULSE TEMP



CASE 3

until the end of the second week in the hospital. Thereafter he improved rapidly and was up and around the ward although still jaundiced ten days before discharge. The lung findings disappeared after the patient had been essentially afebrile for one week. The nuchal rigidity lasted only three days. He was discharged well except for an icteric index of 22 after 45 days in the hospital.

Case No 3 J M (#123582) a nineteen-year-old Negro laborer was admitted to the Cincinnati General Hospital on July 2 1939 complaining of headache, malaise, and muscular pains of five days' duration.

Five days prior to admission this man began to complain of severe

revealed no abnormalities. The heart was normal in size, shape, and position, the rhythm regular, the rate fast, and there were no murmurs. The abdomen was flat and there was marked voluntary splinting of the whole right side. There was hyperaesthesia in the right upper quadrant. No organs or masses were felt until the second day, when the liver became palpable. Peristalsis was normal throughout, and there was no rebound tenderness. The remainder of the physical examination, which included a complete neurological examination, was entirely negative.

On admission, the red blood cells were 3.75 M, hemoglobin, 9.2 grams, white blood cells, 19,000, differential, polymorphonuclears 90 per cent, lymphocytes, 8 per cent, monocytes, 1 per cent, and eosinophiles, 1 per cent. The urine showed ++ albumin, a trace of sugar, large amounts of bile and urobilinogen, occasional hyaline and granular casts, and from two to four pus cells per high power field on a centrifuged specimen. The blood Kahn test was positive. The sputum was thick and rusty, and contained many gram-positive cocci, but no pneumococci could be identified, either directly or by culture in Avery broth or in mice. Lumbar puncture revealed a somewhat elevated spinal fluid pressure (250 mm of H<sub>2</sub>O). The fluid was clear, yellow in color, the Pandy 2+++, and there were 20 lymphocytes per cu mm. Twelve days later the cerebrospinal fluid was normal except for five cells. The spinal fluid Wassermann and gold curve were negative. The icteric index on admission was 175. X-ray examination of the chest revealed a marked increase in the bronchial and peribronchial shadows bilaterally, particularly at the bases. The apices were relatively clear. Repeat examination three days later revealed no change.

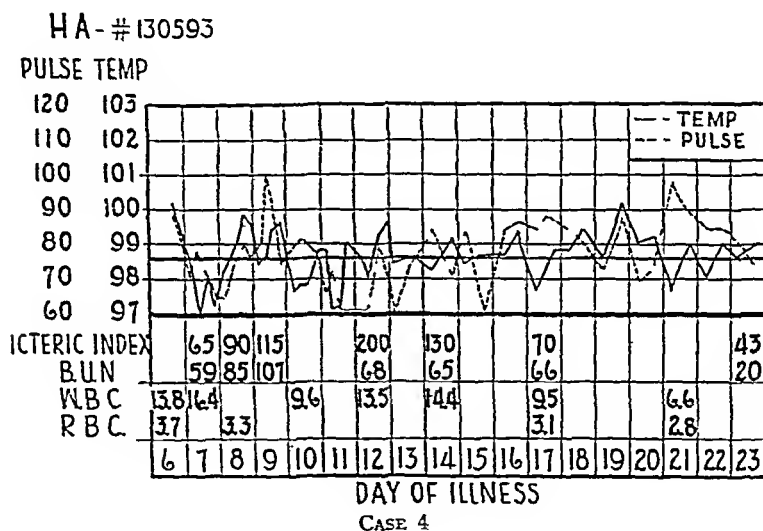
The white blood count rose rapidly to 41,900 on the sixth hospital day, fell to 28,450 on the eighth day, rose again to 49,750 on the ninth day, and then gradually returned to normal on the 15th hospital day. The red blood count dropped to 2.3 M with a hemoglobin of 7.4 grams on the 10th day, and was returned to its original level by transfusion. The urine became normal except for large amounts of bile on the sixth hospital day. It contained urobilinogen throughout his hospital course.

The icteric index rose from its initial level of 175 to 325 on the sixth day, was 300 on the tenth day, 60 on the 20th day, and was 22 at the time of discharge (45th hospital day).

The blood urea nitrogen was 40 on admission and the serum phosphatase was 5.4 Bodansky units. Both returned to normal in the second week.

Examination of the blood serum by the dark field technique was negative for spirochetes. The patient's urine (third week of illness) was injected into guinea pigs and produced no disease. Agglutinations for the *Lepto-*

The patient's temperature and pulse on admission were elevated to 102°F and 120 per minute respectively, and they gradually fell to normal on the sixth hospital day. On the fourth hospital day (ninth day of illness) he became intensely jaundiced and the white count rose to 21,900. On the following day it fell to 13,000, and gradually returned to normal. The icterus gradually subsided over a period of three weeks. At the time of discharge on the twenty-sixth day of illness, there were insufficient numbers of spirochetes in 50 cc of fresh urine to produce disease in a guinea pig, and the patient was entirely well except for slight residual icterus (icterus index 25).



*Case No 4* H A (#130593), a white male laborer aged 21, was admitted to the Cincinnati General Hospital on October 3, 1939, complaining of headache, nausea, and vomiting of five days' duration.

After a meal consisting of a wiener sandwich five days before admission, the patient suddenly developed a severe frontal headache. He soon broke out with sweat, became nauseated, and vomited all he had eaten. Since that time he had been in bed and had been completely unable to eat because of persistent vomiting. That night he became aware of marked soreness and aching in the muscles of his back, shoulders, and legs. The following day he developed generalized abdominal tenderness and pain. On the third day, a cough, productive of a bloody sputum, appeared.



frontal headache and dizziness. Later that same day his throat became sore and he had some difficulty in swallowing. That evening he developed muscle pains in the neck and shoulder girdle. The following day these symptoms increased in severity, and the third day he developed transient diplopia. His legs and back became so stiff and sore that he had difficulty in walking. The throat gradually improved, but the other symptoms, especially the headache, grew worse till the time of admission. No history of chills or fever. At the time of the onset he was employed as a fish-cutter at a local fish house. No history of rat bite, although there were many large rats seen at the fishery. His hands were always wet while working. Rubber boots were worn. This well-developed and well-nourished Negro was admitted to the Medical Service, at which time he appeared acutely but not seriously ill. The vital signs were as follows: Temperature, 102.4, Pulse, 108, Respiration, 34, B P, 112/78.

Skin was normal. There was no icterus. Eyes were normal except for myopia. Head, ears, and nose were normal. Oral cavity normal except for slight injection of the pharynx, tonsils present, though small. There was moderate nuchal rigidity. Lymphadenopathy was present in right epitrochlear, right axilla, and both inguinal regions. The nodes were small and firm. Chest, heart, and lungs entirely negative except for tachypnea and mild tachycardia. Abdomen soft and flat. No organs or masses were palpable. Genitalia normal except for a small condyloma under anterior prepuce. Rectal examination was negative. The extremities were negative except for moderate tenderness over the larger muscle groups. Neurological examination was entirely negative.

On admission, the red blood cells were 4.8 M, Hemoglobin 16.8 gms, white blood cells 9,300, differential normal. Urine was negative. Lumbar puncture revealed normal cerebrospinal fluid under normal pressure. Wassermann was negative. Widal and agglutination for *Brucella melitensis* were negative.

On the fourth hospital day the icterus index was 142, and the white blood cells, 21,950. This latter count fell to 13,000 the following day. The icterus on the eighth hospital day was 114, on the 12th hospital day, 61, and on the twentieth hospital day, 40. Except for large amounts of bile and urobilinogen, the urine remained normal throughout his course.

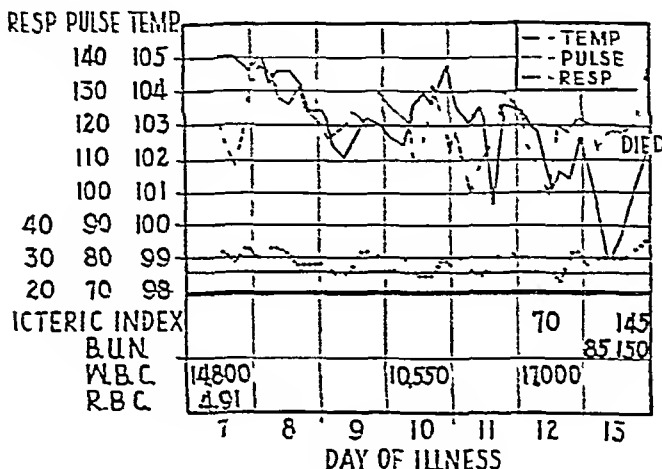
Agglutinations for *Leptospira icterohemorrhagiae* on the eighteenth hospital day were strongly positive in dilutions up to 1:10,000. Dark field examinations of the blood on the eighth day of illness failed to reveal the leptospira in the blood. Guinea pigs inoculated with the sediment of fresh urine on the 25th day of illness did not develop Weil's Disease.

the patient began to void and from then on his course was one of gradual recovery. The blood urea nitrogen and icteric index gradually fell to normal by the 52nd day after admission to the hospital. The urine and the spinal fluid cleared and recovery was complete.

At the time of the anuria the patient had a diffuse papular erythematous skin eruption but we were unable to say with certainty that it was part of his disease and not a drug eruption (he had been given pentobarbital).

He was discharged still slightly jaundiced on the 33rd hospital day. One week later he had a relapse characterized by sudden onset of headache, nausea, and vomiting. This lasted two days and was followed by complete

RT- = 125293



CASE 5

recovery. He has been seen many times since and is quite well. Seven weeks after the onset of his disease the patient's blood serum agglutinated the leptospira icterohemorrhagiae in dilutions of 1:100,000, with an even higher lytic titer. Repeated Wassermann tests since therapy are negative.

*Case No 5* R T (≈ 125293) a thirty-one-year-old Negro laborer, was admitted to the Cincinnati General Hospital on July 19, 1939, complaining of severe headache and high fever of six days' duration.

During the three weeks prior to admission this man had had a "mild head cold" with a non-productive cough. On July 13, 1939, six days

On the day before admission, dark urine and rapidly increasing jaundice appeared. There was no chill, and he was not aware of fever. On the day of admission he had a rather severe epistaxis. No history could be obtained of exposure to rats or infected water.

The patient was a well-developed and well-nourished white man of 21, who was deeply icteric, somewhat lethargic, and markedly prostrated. His vital signs were: Temperature, 100.4°, Pulse, 90, Respiration, 28, B P, 110/70. Save for jaundice, the skin was negative. There was rather severe conjunctivitis of both orbital and palpebral conjunctivae. The pharynx showed moderate inflammation and some old blood. No nuchal rigidity could be detected, and there was no lymphadenopathy. The chest was symmetrical and expanded well. The lungs were clear and the heart was normal. The abdomen was flat and exquisitely tender in all quadrants. There was much voluntary resistance, but no true muscle spasm. No organs or masses could be palpated. Costovertebral tenderness was pronounced bilaterally. The extremities showed only muscle tenderness most marked in the calves, and the neurological examination was negative.

On admission, the laboratory data showed RBC, 3.74 M, Hgb, 12.0 grams, WBC, 13,800. The differential showed 85 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophiles. The dark amber urine was strongly acid, and showed + + + + albumin, a trace of sugar, occasional WBC, no RBC or casts, and strongly positive tests for bile and urobilinogen. The benzidin test was faintly positive. The sputum was muco-purulent and showed both new and old blood. No pneumococci were found. The blood and spinal fluid Wassermann tests were negative. Icteric index, 65, blood urea nitrogen 59 mgm per cent, CO<sub>2</sub> combining power 50 vol per cent, blood cultures were negative. Dark field examination of the blood on the third hospital day showed motile spirochetes. The spinal fluid was under normal pressure and showed 34 cells, half of which were polymorphonuclear leukocytes. Prothrombin time was 15 seconds.

At no time in his course was the patient's temperature above 100.5°. He was oliguric on admission, and in the next two days he became completely anuric. The icteric index rose during this time to 115, and the blood urea nitrogen to 108 mgm per cent. After 30 hours of complete anuria, as determined by catheterization, he was given 500 cc of whole blood from a compatible donor who had recently recovered from Weil's Disease (Case No. 2). The blood used had an agglutination titer against *Leptospira icterohemorrhagiae* of better than 1:30,000. Within six hours

both lung bases on the sixth day and he died without regaining consciousness on the morning of his seventh hospital day

*Case No 5 Autopsy Number N-39-334* The necropsy was performed 11½ hours post mortem The body was that of a well-developed and slightly obese black male of about thirty years of age The skin of the palms of the hands and the soles of the feet had a distinctly yellow cast The eyes appeared swollen and injected, and there were small collections of fluid beneath the bulbar conjunctivae The sclerae were greenish-yellow There was a quite profuse greenish-yellow watery discharge from the nose and the mouth

The thoracic and the abdominal organs were in their normal relationships and the pleural and peritoneal surfaces were smooth and glistening and free of adhesions All the organs and tissues which are normally light in color showed evidence of yellow staining

*Heart* The smooth, brownish-red heart weighed 475 grams and was of a flabby, dishrag consistency On section, the soft myocardium was pale red and appeared toxic The gross impression of a toxic myocardiosis was confirmed microscopically but there was in addition a superimposed acute myocarditis The muscle fibers were fragmented, swollen, and granular These changes, as well as smaller amounts of hyaline degeneration and actual necrosis rarely involved fibers in their entirety but were limited to small segments There was karyolysis of a fair proportion of the nuclei There was a diffuse infiltration of reacting cells into the interstitial tissues and very occasionally into one of the broken-up muscle bundles These cells were chiefly leukocytes and mononuclear cells, but a moderate number of lymphocytes were also present There were quite dense accumulations of lymphocytes as well as plasma cells around the blood vessels and particularly beneath the endocardium

*Lungs* The right lung weighed 910 grams and the left 850 grams The lungs were purplish-blue and red, and were fairly firm and sub-crepitant, although some areas were entirely devoid of air On section, the lungs were dark gray and purple with scattered irregular areas of pink and red The dark purple portions were wet and tough whereas the red areas were more dry, friable, and slightly granular Microscopically there was pronounced pulmonary edema, pale, pink, granular material filling the majority of the alveolar spaces There were scattered patchy areas of hemorrhage in the alveoli, the red blood cells being enmeshed in strands of fibrin in many instances Recent areas of hemorrhage without any fibrinous exudate were also in evidence In the hemorrhagic portions the alveolar walls

before admission, while operating an air drill on a gas main construction job, he suddenly noted severe frontal headache and nausea. These symptoms became rapidly worse, he felt feverish, and had to quit work. He was at home in bed until the time of his admission. The headache grew worse and he had marked drowsiness. The nausea did not persist except when he tried to sit up. There was no vomiting. Anorexia became very marked. He became very constipated, and on the fourth day of his acute illness he took some Senna leaves which resulted in a severe diarrhea which persisted until the time of admission. There was no blood or mucus in the stool. There was no history to suggest typhoid fever or dysentery, and he was unaware of the presence of rats where he worked. This large, muscular Negro was admitted to the Medical Service acutely ill and in a stuporous state. His vital signs were: Temperature, 105°, Pulse, 124, Respiration, 28, B P, 130/94. His skin was hot and dry, and there was no evidence of jaundice. There were a few moist rales heard at the right lung base, but the rest of the physical examination was astonishingly without abnormality.

On admission, the red blood cells were 4.91 M, with 11.0 grams Hgb, white blood cells were 14,800, with a normal differential. The urine was entirely negative. The spinal fluid examination revealed an initial pressure of 220 mm of H<sub>2</sub>O and contained three lymphocytes. Blood culture and blood Wassermann were negative. Agglutinations for typhoid, brucellosis, and dysentery, were negative. X-ray of the chest revealed no abnormalities. The white blood count fell to 10,000 on the fourth hospital day, and rose again to 17,000 on the sixth day. The urine showed ++ albumin on the third hospital day. On the sixth hospital day, large amounts of bile were found in urine. The icteric index was found to be 70 on the fifth day, and 145 on the seventh day. The CO<sub>2</sub> combining power was 24 volumes per cent on the sixth day, at which time the blood urea nitrogen was 85 mgm per cent. This latter rose to 150 terminally. The blood sugar was approximately 200 mgm per cent on several occasions. The cells in the spinal fluid rose to 20 on the fourth hospital day, of which 60 per cent were polymorphonuclear leukocytes. The spinal fluid protein was never elevated. Direct examination of the blood and agglutinations revealed no evidence of spirochetal infection.

The patient's temperature diminished slowly throughout his illness, and his only complaint was frontal headache. He became increasingly drowsy. An icteric tint was noted in the sclerae on the third hospital day, and this rapidly increased to marked jaundice. He rather abruptly became anuric on the fifth hospital day, and lapsed into coma. Pneumonia was found at

granular material and cellular debris, together with mononuclear cells and rare polymorphonuclear leukocytes. There were a moderate number of large, dilated tubules the lumina of which were completely filled with necrotic desquamating cells and endothelial leukocytes together with regenerating epithelial cells, many of which contained mitotic figures. There was acute and subacute interstitial nephritis, which was primarily focal and localized largely in the pyramids. A slight diffuse interstitial infiltration was present, however. The cells consisted chiefly of lymphocytes with a varying proportion of polymorphonuclear leukocytes, mononuclear and plasma cells in different areas. There were numerous and well-defined nests of lymphocytes, and the cellular reaction was particularly marked around the vessels and lymphatics close to the renal pelvis. Interstitial edema was quite pronounced in this region also. The glomeruli were normal.

*Suprarenals* The medullary portions were disintegrating and only small particles of soft gray material were left clinging to the thin yellow cortices. In the left suprarenal the medullary space was distended and filled with a fairly large dark blood clot, but there was no hemorrhage in the right suprarenal. No other changes were noted microscopically.

*Mesenteric* There were small areas of hemorrhage scattered throughout its substance.

*Brain* The brain weighed 1 260 grams. There was some thickening of the meninges over the left fronto-parietal region. In the right occipital region there was an area of subarachnoid hemorrhage which measured about 1.5 centimeters in diameter. The basilar meninges were slightly thickened. There were distinct Kernohan's notches on both sides and a definite cerebellar pressure cone.

The brain was cut at 1.5 cm thicknesses and nothing remarkable was discovered except for some destruction of the central white matter which was obviously due to post mortem change. Multiple sections through the brain stem and cerebellum were also negative.

Microscopic sections from the uncinate and motor areas stained with cresyl violet were on the whole not significant. There was some chromatolysis, and an occasional nerve cell showed neuronophagia. In the white matter of the frontal lobe, portions of the tissue failed to take the stain and in these areas there were large numbers of *B. treich* (post-mortem changes).

Sections of the cortex from the motor and pre-motor areas were stained with hematoxylin and eosin. There was thickening of the meninges in both of these areas, more so in the pre-motor than in the motor areas.

were packed with polymorphonuclear leukocytes, and the alveoli in these regions also contained polymorphonuclear leukocytes and pigmented macrophages in varying degrees of concentration. The general picture was that of an acute hemorrhagic lobular pneumonia. The bronchi of both lungs contained a brownish, sticky, viscid exudate, but microscopically their lumina contained only a few reacting cells and there was only slight involvement of the walls by an acute inflammatory process.

*Liver* The smooth, swollen, flabby, light brown liver weighed 2,575 grams. There were several soft, bulging areas on the superior surface which were almost fluctuant. On section, the liver substance was homogeneous and pale brown with obliteration of the vascular markings. The markedly softened areas represented merely soft, flabby, hepatic tissue. Microscopic examination revealed a severe toxic hepatitis with a moderate degree of central zone necrosis. The liver cords were fragmented and deranged with dissociation of the cells. Many of the nuclei were swollen and the cytoplasm showed a fine diffuse fatty degeneration. The outlines of numerous cells were fuzzy, and the nuclei were either indistinct or had disappeared completely. The perisinusoidal lymph spaces were very wide and prominent. There was a well-marked lymphocytic infiltration throughout the tissues of many of the portal areas, which bore no striking relationship to the bile ducts. Any positive evidence of attempted regeneration was lacking. There was some suspicion of bile retention.

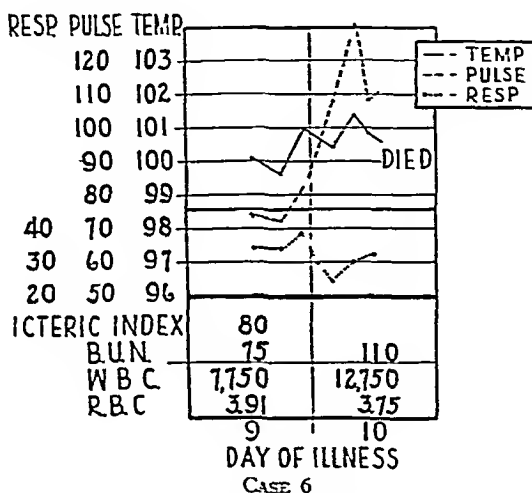
*Spleen* The smooth, flabby spleen weighed 200 grams. On section, the purplish-black pulp was extremely pulsatous, very wet, and coarsely granular. Microscopically there was marked congestion and such a decided increase of polymorphonuclear leukocytes as to justify the diagnosis of acute splenitis.

*Kidneys* The kidneys were large and flabby, the right weighing 350 grams and the left, 375 grams. Their thin transparent capsules stripped easily, revealing smooth, reddish-brown surfaces which were speckled with numerous small, red dots. On section there was bulging of the pale tan cortices and eversion of the cut edges. The medullae were even paler than the cortices, and possessed irregular, purplish-red borders. Microscopic sections revealed acute toxic nephrosis which was confined chiefly to the epithelium of the convoluted tubules. These cells were swollen in nearly all instances so that their margins, bordering the tubular lumina, presented a scalloped or markedly ragged appearance. In many instances the tubular epithelium was definitely necrotic with desquamation into the lumen, and either fading or complete disappearance of the nuclei. The lumina of the convoluted tubules were generally narrowed, and frequently contained red,

The pancreas, gastro-enteric tract, bladder, and ureters were normal. There was chronic interstitial prostatitis, probably unrelated to other pathological changes in the case.

Occasional spirochetes, morphologically characteristic of *Leptospira icterohemorrhagiae*, were found in Levaditi preparations of the kidney and liver. They could not be demonstrated in the suprarenals, spleen, lungs, or brain. The spirochetes found in the kidneys were not numerous and were found in the interstitial tissues as well as in the epithelium of the convoluted tubules.

E.F. - # 130453



Case No 6 E F (#130453), a white male, aged 65, sewer-worker, was admitted to the Cincinnati General Hospital on September 30, 1939, complaining of generalized pain of eight days' duration.

The history was difficult to obtain because of the extremely exhausted state of the patient. As nearly as can be determined, the patient suddenly developed severe, prostrating malaise eight days prior to admission. The following day he complained of a severe epigastric and right upper quadrant pain. On the third day, with increasing prostration, he became extremely short of breath, had complete anorexia, and occasionally vomited. Two days before admission he became aware of jaundice. There was no history of chill, headache, or cough, but patient had been aware of fever for approximately one week. No further history was obtainable from the patient. Some relatives volunteered the information that the patient had been working in a sewer two weeks before the onset of his illness.



There was an increase in arachnoid cells, and an accumulation of reactive cells in the meninges, consisting chiefly of mononuclear cells and a moderate number of plasma cells. A few small lymphocytes and an occasional polymorphonuclear leukocyte were also seen in the exudate. In the parenchyma the perineuronal and perivascular spaces were wide and there was congestion of all the vessels. Sections of the pons and medulla stained by this method showed little besides congestion. There was some fat in the cells of the olives, but most of the cells contained nuclei. Sections of the cerebellum showed a striking generalized loss of cells throughout the granular layer. There was no reaction in the granular layer and the nature of the process was not clear. There was possibly some slight reduction in the number of Purkinje cells, and there was a proliferation of the glial nuclei in the Purkinje cell layer. A moderate number of small lymphocytes were seen in several of the perivascular spaces in the white matter. The meningeal exudate was not as marked in this region as in the cortex.

Scarlet R fat stains of the two areas from the cerebral cortex, from the cerebellum through the dentate nucleus, from the mid-pons, and from the lowermost extent of the medulla, revealed no abnormalities. There was some accumulation of fat in the cells of the dentate nucleus.

Sections from two cortical areas, from the cerebellum through the dentate nucleus, from the mid-pons, and from the region of the decussation of the pyramids in the medulla, were stained by the Smith-Quigley method. These showed spotty demyelination which was rather marked in the pyramidal fibers in the pons, as well as in the fibers of the pons itself. There was some spottiness also in the brachium conjunctivum, and in the white matter of the cerebellum there was streaky demyelination just opposite the dentate nucleus. In the cortex this demyelination was also streaky and was not confined to perivascular spaces. Similar sections were stained by the Loyez myelin sheath method (to check the above findings) and revealed no myelin sheath abnormality.

Sections of the cerebellum stained after the method of Gros and Bodian revealed the loss of granular cells and an increase in glial nuclei in the Purkinje layer.

Sections from the medulla through the greatest extent of the inferior olive were stained with cresyl-violet and hematoxylin and eosin, and there was nothing to add to previous descriptions, with the single exception that the cells in the inferior olive were all markedly degenerated at this level. The cells which remained showed up only as small collections of fat with no nuclei. There was an increase in glia in the region of the inferior olive. The cells of the reticular formation and of the hypoglossal nucleus, a few of which were seen at this level, showed some loss of Nissl substance.

*Heart* The soft flabby, reddish-brown heart weighed 450 grams. There was moderate dilatation of all of the chambers. On section the cardiac musculature was homogeneous but flabby and pale reddish-brown. The coronary arteries showed a moderate amount of sclerosis. Microscopic examination confirmed the coronary arteriosclerosis and showed in addition a well-marked diffuse myocardial fibrosis. There was also fragmentation of many of the muscle bundles and the cytoplasm of these took the stain unevenly and presented a rather granular appearance. The number of hours post mortem however does not allow these findings to be interpreted as definite evidence of toxicity particularly since many of the fibers appeared normal with good preservation of their cross-striations.

*Lungs* The external surfaces of the voluminous lungs presented a mosaic of dark purplish-red and black. The right and left weighed 1175 grams and 1100 grams respectively. On section, the lungs dripped blood, and scattered throughout the dark, red moist sub-crepitant lung tissue there were many large, lumpy, friable areas which were entirely devoid of air. Microscopically there was marked pulmonary congestion and edema, the normal mesh-work of the lungs being obscured by the pools of fluid and the accumulations of erythrocytes that filled a majority of the alveolar spaces. Interlacing strands of fibrin and a moderate number of polymorphonuclear leukocytes scattered through the alveoli made positive the gross impression of hemorrhagic lobular pneumonia. The cellular response was patchy and there were relatively few massive aggregations of polymorphonuclear leukocytes. The pneumonic process appeared to be an early one. Although the bronchi contained reddish mucoid material and appeared to have reddened mucosal linings there was little evidence of inflammation in their walls.

*Liver* The pale brown liver weighed 1850 grams. On section there was bulging of the substance above its capsule with rolling of the cut edges. The hepatic tissue was finely granular and yellowish-brown with numerous paler yellow blotches scattered throughout. The organ was quite friable and felt greasy. Microscopic studies revealed a severe toxic hepatitis with marked degeneration of the liver cells around the central veins and to a lesser degree about some of the portal areas. There was a marked rarefaction of the cells in the central portions of the lobules, many of the cells having disappeared completely while those that remained were partially fragmented and shrunken. Degenerating liver cells could easily be found within the lumina of the central and portal veins. The hepatic damage was of a rather spotty distribution, some areas presenting a relatively normal appearance. There were focal areas of fatty infiltration. The perisinusoidal spaces were swollen and prominent. There was quite marked

This elderly man in a semi-stuporous state, severely orthopneic, was obviously dangerously ill. His vital signs were Temperature, 100°, Pulse, 75, Respiration, 35, B P, 120/60. His skin and sclerae showed obvious jaundice, and there were numerous purpuric spots scattered over his body. There was a cataract in the left eye, and a pterygium in the right. The tongue was red and coated with a thick, black material which did not rub off. The pharynx was negative and there was no nuchal rigidity. Aside from dry asthmatic wheezes throughout both lung fields, the chest was normal. Heart could not be accurately percussed. Heart sounds were distant and of poor quality, and the rhythm was grossly irregular. The abdomen was slightly distended and there was tenderness throughout the right upper quadrant. The liver was palpated three centimeters below the costal margin. No other abdominal masses could be palpated. The prostate was moderately enlarged bilaterally and was quite firm. Except for the purpura, the extremities were normal, as was the neurological examination.

Laboratory findings were RBC, 3.91 M, Hgb, 11.6 grams, WBC, 7,750, Differential normal. The dark amber urine was strongly acid, showed a trace of albumin, occasional RBC and WBC, and gave positive tests for bile, urobilinogen, and blood. The blood urea nitrogen was 75 mgm per cent, CO<sub>2</sub> combining power was 26 vol per cent, icteric index was 80. Prothrombin time was 15 seconds. Blood cultures were negative. Electrocardiograms showed ventricular tachycardia and evidence of severe myocardial damage. An X-ray of the chest taken early on the second hospital day showed slight cardiac enlargement, elongation of the aorta, and a marked increase in the broncho-vascular markings in both hila. There was minimal evidence of pneumonic infiltrate at the left base.

The patient's condition remained critical throughout his hospital course. His temperature was never high. In spite of forced fluid administration, the blood urea nitrogen rose to 110 mgm per cent and the CO<sub>2</sub> combining power remained low. The pulse rate rose to 140 and the patient died 27 hours after admission to the hospital, with a blood urea nitrogen of 175 mgm per cent. At death a large amount of blood ran from his mouth.

*Case No 6* Autopsy No N-39-423. The necropsy was performed 19 hours post mortem. The body was that of a well-developed and well-nourished elderly white man who appeared about 65 years of age. The skin, mucous membranes, and sclerae were bright yellow in color.

The thoracic and abdominal organs were normal in their relationships. The pleural and peritoneal surfaces were smooth and glistening and free from adhesions or exudate.

- 1 A congestion of the cerebral vessels throughout both the white and the gray matter, which was present in all sections,
- 2 Cortical atrophy, and
- 3 Cerebral arteriosclerosis in the meningeal vessels cut in cross-section

Sections stained with hematoxylin and eosin showed thickening of the meninges and a slight increase in the arachnoid cells. An exudate was present which consisted chiefly of mononuclear cells, a moderate number of polymorphonuclear leukocytes, and an occasional lymphocyte. These findings were also present in the meninges of the cerebellum and around the brain stem. A survey of the cerebellum indicated that there was a mild outfall of cells in the granular layer as well as an increase in the glial nuclei in the molecular layer of the cortex. There was congestion of the vessels in all the sections, especially in the medulla. There appeared to be some fat in the cells of the olives and of the dentate nucleus.

Cresyl-violet stains of cortical blocks showed chromatolysis in the nerve cells of the cortex and there was an occasional example of neuronophagia.

Scarlet R stains showed a moderate amount of fat in the cells of the dentate nucleus, and some fat in the phagocytic cells of the white matter, but in the latter fat was extremely scarce. The cells of the cerebral cortex and those of the cerebellum appeared normal by this method.

Many sections from the cerebellum and from several cortical areas were stained by the Bodian and Gros methods, and the only abnormality revealed was an increase of glia in the molecular layer of the cerebellum.

Jahnel and Levaditi stains revealed no structures that could be definitely identified as spirochetes.

The pancreas, except for moderate fatty invasion, appeared normal. The urinary bladder, ureters, and the gastro-enteric tract appeared normal.

There was generalized arterio- and arteriolar sclerosis.

The prostate showed benign adenomatous hyperplasia and chronic interstitial prostatitis.

Levaditi stains of the kidney, lungs, liver, spleen, and suprarenals revealed the *Leptospira icterohemorrhagiae* only in the kidneys. The organisms were sparsely scattered through the kidneys, and the finding of more than two organisms in any microscopic field was rare. They were present in the epithelium of the convoluted tubules and also appeared within the interstitial tissues.

Doctor Charles D. Aring made an extensive study of the pathological changes in the brains of these two cases, and we are indebted to him for a large part of the microscopic findings.

inflammatory reaction in the portal triads consisting of lymphocytes, plasma cells, and occasional polymorphonuclear leukocytes—the type of cells and their relative proportions resembling the reaction found in the kidneys. Apparently no attempt at regeneration was being made. There was little evidence of bile retention even in the central areas.

*Spleen* The soft, dark red spleen weighed 275 grams. On section, the splenic pulp was creamy red and mushy. Microscopically, there was pronounced congestion and marked invasion of the pulp by polymorphonuclear leukocytes.

*Kidneys* The similar-sized kidneys, together, weighed 550 grams. Their thin capsules stripped with ease, revealing pale brown surfaces. On section, there was eversion of the cut edges, and the pale, friable cortices and medullae were poorly demarcated from each other. A severe toxic necrosis was found on microscopic examination. The epithelium of the tubules, particularly of the convoluted tubules, showed marked cloudy swelling, with ragged, granular, disintegrating cells and karyolysis. In spite of the number of hours post mortem, these changes were thought to be too pronounced to be accounted for by this factor alone. There was a diffuse cellular reaction throughout the interstitial tissues, consisting of collections of lymphocytes, plasma cells, and a moderate number of polymorphonuclear leukocytes. The reaction appeared acute and was present in the cortices and the pyramids, but was more pronounced in the former. There was a slight increase of young connective tissue accompanying the inflammatory reaction, particularly about some of the glomeruli, and in these areas the tubules were diminished in number, some of them having either partially or completely disappeared. There were a few scarred glomeruli, and the arteries and arterioles showed a moderate amount of hyaline thickening.

*Suprarenals* On section, the tan cortices were well differentiated from the dark brown, mushy medullae. Microscopically there was noted degeneration of the medullary areas and the presence of small nests of lymphocytes scattered through the cortices. There were also small focal extravasations of erythrocytes in the remnants of the medullae.

*Brain* The brain weighed 1325 grams. The arachnoid over the superior aspect of the cerebral hemispheres and in the left Sylvian fissure, although fairly transparent, was thickened and gelatinous. The meninges elsewhere appeared normal. There was a small Kernohan's notch on each side, and a marked cerebellar pressure cone.

Multiple coronal sections were made through the brain at 1.5 cm thicknesses. Grossly these were entirely negative except for the following points:

merely a reparative attempt on behalf of the damaged myocardium. The pronounced accumulations of lymphocytes and plasma cells beneath the endocardium are particularly interesting in view of the two cases of vegetative endocarditis reported by Drägers (72) the spirochete being positively identified within the heart in one of these. This case also had large accumulations of cells beneath the endocardium. It may well be reasoned that if sufficient time had elapsed before death in Case No. 5 the subendocardial inflammatory process might have broken through the endocardium and have been identified grossly. The cellular reaction in the heart was quite similar to that found elsewhere. The myocardium certainly showed severe toxic damage and although this is common in severe toxemias the vacuolization, loss of striations and hyalinization of portions of muscle bundles are suggestive of injury of a type that is rather characteristic of the muscular damage that occurs in Weil's Disease.

Hepatic damage was severe in both cases and apparently varying degrees of cloudy swelling, rarefaction and dissociation of the cells, or actual necrosis are present in nearly all cases. Although hepatic damage has generally been considered the cause of the jaundice in Weil's Disease the exact mechanism of its production has remained in doubt. Swelling of the hepatic cells together with functional impairment due to toxic injury has been advanced as the cause but Oka (64) believes that dissociation of the cells with consequent rupture of the bile capillaries is responsible. Attempts at regeneration although reported as a fairly constant finding, were not demonstrable in either of the present cases. Neither was there much evidence of biliary stasis but some of the cells around the central veins did contain orange-brown pigment. Cellular infiltration in the portal areas was present in both these cases and has been noted in other necropsy studies.

The central nervous system in Weil's Disease has received only a moderate amount of attention. Meningitis is a well-known complication of the acute stage of this disease and chronic forms have been described. Murgatroyd (42) reports a case in which the spirochete was recovered from the spinal fluid as long as six months after the onset of the patient's illness. Haschec and Tobey (44) have also recently reported a case in which the meningeal signs and symptoms

COMMENT ON THE PATHOLOGY OF THESE TWO CASES WITH REFERENCE  
TO THE USUAL MORBID ANATOMY OF WEIL'S DISEASE

A review of the pathological findings in these two cases of Weil's Disease reveals evidences of an acute generalized infection with an accompanying profound toxemia. The similarity of the findings in the two cases is rather striking. The chief morphologic changes were present in the kidneys, liver, and lungs.

Damage to the capillaries was manifest by the hemorrhagic condition of the lungs, in both cases, and by the hemorrhage which occurred in the left suprarenal and in the subarachnoid space, together with the focal areas of hemorrhage in the mesentery of Case No. 5. The hemorrhagic tendency was apparently not so pronounced in Case No. 6, the only other hemorrhages besides the pulmonary manifestations being present in the suprarenals, and these were quite minute. Hemorrhage within the suprarenals is of common occurrence in this disease, being reported frequently in other necropsy studies.

The hemorrhagic condition of the lungs has been reported previously, but occurs most characteristically in the guinea pig, where the lesion is typical and practically universal. Focal pneumonic lesions have also been described but are not common. Certainly the pulmonary inflammatory reaction in the two cases reported here was patchy and early, and some of it may well have been a response to the hemorrhage, but it is believed that not all of it could be accounted for by this factor alone. The kidneys of both cases illustrate the known fact that the tubules bear the brunt of injury. The tubular damage, interstitial edema, and inflammatory reaction, are as typical as any of the findings in this disease, the pathologic picture of which is not sufficiently definite and clear-cut to enable a diagnosis to be made by the morphologic changes alone. The acute interstitial nephritis is said to be confined chiefly to the cortical areas in most cases, but was quite diffuse in both of these cases and involved the cortex more markedly in one and the pyramids in the other.

The heart in Weil's Disease sometimes shows very interesting changes. The heart in Case No. 6 may be considered essentially negative from the standpoint of this specific disease. The heart in Case No. 5, however, presented definite damage, the cellular reaction was quite marked throughout and certainly indicated more than

hemorrhages elsewhere. Microscopic examination revealed acute toxic nephrosis and focal areas of hepatic necrosis. No inflammatory reaction was noted in the kidneys but fairly numerous polymorphonuclear leukocytes were seen in the sharply defined, necrotic areas in the liver. The remaining liver cells also appeared swollen and granular. It is interesting that the portal areas showed an infiltration of lymphocytes, and mononuclear cells with occasional polymorphonuclear leukocytes, a cellular reaction similar to that found in the same areas in the human livers.



CASE 7. Photomicrograph of guinea pig liver showing *L. icterohemorrhagiae* in the tissue. This animal was infected with the urine from Case No. 7.

The focal hepatic necrosis is apparently more common in guinea pigs with Weil's Disease than in human beings, but Ball (96) reported a similar picture in his case and it has been noted by others.

Levaditi preparation of the liver and kidneys showed many spirochetes which were most numerous in the liver.

Case No. 7. W. D. (140434), a colored male, aged 20, W. P. A. laborer, was admitted to the Cincinnati General Hospital on March 10, 1940, in such a confused mental state that he could not give a history. From a relative we were able to ascertain that he had been taken suddenly ill with



were severe. The clinical and spinal fluid findings in Weil's Disease have not been well related to pathologic changes. Dragert (72) studied the central nervous system in three cases, and in one of these the meninges of the brain and spinal cord showed a cellular infiltrate consisting of lymphocytes and plasma cells. The same author also noted an icteric discoloration of the ependyma and spinal fluid, which he explained on the basis of damage to the meninges due to the inflammatory and toxic process which allowed passage of the pigment from the blood to the spinal fluid. In the present two cases these changes were not found, but the meninges in both showed an inflammatory reaction, as has been described. Dragert (72) also noted petechial hemorrhages and focal aggregations of lymphocytes and plasma cells in the tibial and brachial nerves, but no degeneration of the nerves themselves. Kaneko (63) observed changes in the nerve cells, but Dragert (72) did not. He did describe glial proliferation in the thalamus, however. The neuronal changes in the current cases have been described in some detail. Although an exact interpretation of the neuronal changes is not possible, certainly these, together with meningeal reaction, bear further testimony that Weil's Disease is a generalized disease and that the central nervous system is by no means immune. No actual inflammatory reaction was observed within the brain substance, but the cellular response in the meninges was identical with that found elsewhere.

Intraperitoneal inoculation of infected cerebrospinal fluid, blood, or urine, into guinea pigs, produces the characteristic lesions in from five to ten days. Urine from Case W D, Number 7, was injected intraperitoneally into a guinea pig during the second stage of the patient's illness, and another pig was inoculated with urine obtained during the patient's convalescence. The first pig died on the thirteenth day and the second pig was sacrificed on the eleventh day in a markedly toxic state. These animals at necropsy were intensely jaundiced, the icterus being particularly noticeable about the ears, nose, soles of feet, and genitalia. There were punctate hemorrhages scattered throughout the skin, subcutaneous tissues, and peritoneum, and practically every organ presented multiple hemorrhagic areas. The punctate pulmonary hemorrhages are usually particularly characteristic, but in these animals they were no more marked than the

grateful to Doctor R. E. Dyer and his staff, particularly to Doctor A. Packchianian for the co-operation they have given us in establishing the diagnosis in our cases. We hope that we may stimulate sufficient interest in this disorder to make the creation of more diagnostic laboratories mandatory.

### SUMMARY

- 1 The more important items of the world literature on Weil's Disease are reviewed
- 2 The clinical and diagnostic features of the disease are discussed in detail
3. Seven case reports are given <sup>4</sup>

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<sup>4</sup> An eighth case has recently been proved by Dr. Rob't Woolson at the Cincinnati General Hospital. Another with a classical picture, a female child and no autopsy could be obtained so it cannot be proved. It was uncovered from one 1938 hospital record. A teach is now being used.

headache, nausea, and vomiting, eight days prior to admission, and had grown steadily worse. Three days before admission he became jaundiced and stuporous.

He was practically afebrile on admission, and aside from jaundice, muscle tenderness, and his semi-stuporous state, little was found on examination.

As in the previous cases, the findings included leukocytosis, urea retention, increased icteric index, cells and increased protein in his spinal fluid, normal prothrombin time. His course was typical and uneventful without other than supportive therapy. He is well and working at the present time.

His urine produced fatal jaundice in guinea pigs in the first part of the third week of his disease, and later (the sixth week of the disease) positive agglutinations for *L. icterohemorrhagiae* were obtained in dilutions of 1:10,000. This strain differed somewhat from that found in the previous six cases, and gave a simultaneous agglutination to *L. canicola* in a titer of 1:1,000. Further serological studies on this case are still being carried out.

#### COMMENT

Weil's Disease, like typhoid fever, is an acute and serious infection, protean in its manifestations. It has been diagnosed much less frequently in this country than elsewhere in the world. We are not convinced that this discrepancy is due solely to a remarkably lower incidence of the disease in this country, and have therefore taken the liberty of discussing this disease, now 54 years old, in detail.

We have not attempted to cover all of the world literature, but only that which should contribute to more frequent proper diagnosis of the disease in this country. We have attempted to emphasize both the clinical and laboratory methods of diagnosis, and have included seven detailed case reports which demonstrate most clearly the variability which this disorder may show.

Weil's Disease is primarily an occupational disease now compensable in New York State, yet, there is not available to the medical profession the proper therapeutic agent—immune serum. This agent will not become available until the importance of the disease and its high mortality rate—30 per cent, is recognized in this country.

The National Institute of Health at Washington, D. C., is the only public laboratory in the country adequately equipped to do thorough diagnostic and investigative studies on this disease.\* We are deeply

\* There are several private and university laboratories now so equipped.

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# THE ACTION OF FLUORINE IN LIMITING DENTAL CARIES

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Incidental to the establishment of fluorine in the drinking water as the cause of mottled enamel (1, 2, 3), some observations were made of the occurrence of dental caries. These indicated that mottled teeth were somewhat less carious than the non-mottled teeth. None of the studies attempted to establish a direct relationship between the fluorine content of the water and the occurrence of dental caries. Quite recently three types of investigation have indicated that such a relationship might exist and that fluorine might act to reduce the activity of dental caries independently of its effects in producing mottled enamel. The work pointing to this conclusion consists of a) field studies of the relationship of mottled enamel and fluorine intake to dental caries, b) chemical analyses of the teeth, and c) experiments with coarse particle caries in rats. This paper reviews the work under these three heads and records and analyzes recent experiments designed to show the mechanism by which fluorine influences dental caries.

## I EVIDENCE THAT FLUORINE INFLUENCES ACTIVITY OF DENTAL CARIES FIELD STUDIES

In his work on mottled enamel Black (4) suggested that caries incidence was reduced where the condition was endemic. He states

As to caries, the teeth of these children compare favorably with those of other communities where endemic mottled enamel is unknown.

But when the teeth do decay the frail condition of the enamel makes it extremely difficult to make good and effective fillings. For this reason many individuals will lose their teeth though the number of carious cavities is fewer than elsewhere'. Although MacKay (5) made no attempt to compare the caries susceptibility of people of



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caries-free, whereas 22 per cent of the children using a water supply containing 1.7 to 2.5 p.p.m. of fluorine had no caries. Since it was also noted that, when water with a high fluorine content was being used, the caries incidence in mottled and normal teeth was not significantly different, it was concluded that the limited immunity-producing factor present in the water is operative whether or not the tooth is affected by mottled enamel." In another survey (10) in Illinois, which was designed to show the relationship between fluorine content of the drinking water and the occurrence of dental caries, it was found that in two cities (Galesburg and Monmouth) which had water supplies containing respectively 1.8 and 1.7 p.p.m. of fluorine the occurrence of caries was less than in two other cities (Macomb and Quincy) which used water containing only 0.2 p.p.m. of fluorine. While the total caries incidence per one hundred teeth in the first two cities (201 and 205) may not be significantly less than that in the last two (401 and 638), the differences in its occurrence in the upper anterior teeth were striking. In these teeth there were only 0.67 and 0.38 cavities per one hundred tooth surfaces in the children using the fluorine-containing waters, whereas in those using the other waters there were 7.2 and 9.3 per 100 surfaces.

That fluorine in the water is particularly effective in reducing the caries in the upper anterior teeth is substantiated by the observations of Aram, Aberle and Pitney (11) who were unable to discover any caries in 1,605 permanent incisors in Indian children of New Mexico and Arizona who were using a water supply containing 0.7 p.p.m. of fluorine. Day also failed to find caries in any of 1,352 permanent incisors of his group of children from a mottled enamel area.

The preceding studies seem to show that the reduction of caries noted in association with mottling of the enamel is the result of the intake of fluorine rather than the mottled condition of the teeth *per se*. This is borne out by the observations on deciduous teeth which, although they show little mottling themselves, are particularly resistant to dental caries. Dean (12) is of the opinion that the resistance to caries does not depend upon the presence of fluorine at the time of calcification of the enamel and dentin so much as it does on the fluorine in water used subsequently. The fact that the effects are so much more marked on the anterior teeth than on the molars may be taken

endemic areas with those from other locations, he noted that individuals living in communities which had no mottling of the teeth showed much more caries than did those with mottled enamel, and also that when caries did occur in either the mottled or normal teeth of people in endemic areas, it was limited almost exclusively to the molars. Bunting (6) has observed that the extent and activity of caries was remarkably limited in the mouths of children residing in an area where mottled enamel was common.

More recently indications of the possible relationship between fluorine and dental caries have come from widely scattered sources. Maskai (2) who conducted studies in Japanese provinces observed that "The percentage of dental caries is comparatively small amongst those who suffer from this abnormality" (mottled enamel). In Argentina, Erasquin (1) noted a reduction of caries in the inhabitants of mottled enamel districts. Piperno (7) reported that in Italian villages, those people drinking water rich in fluorine and showing signs of mottled enamel had only about one-tenth of the caries of city inhabitants. Ainsworth (3) studied the effects of the fluoride-containing waters of certain districts in England upon the teeth of children. In a group of two hundred children from five to fifteen years old, both the permanent and deciduous teeth showed a low caries incidence. Of the permanent teeth, 7.9 per cent, and of the deciduous teeth, 12 per cent, were carious compared with respective averages of 13.14 per cent and 43.3 per cent for the rest of England. It is of particular interest to note that although deciduous teeth showed scarcely any signs of mottling they manifested the greatest reduction in caries. Day (9) has recently reported similar observations from India where he found 41.89 per cent of the children in a mottled enamel area free from caries compared with only 5.95 per cent in a non-endemic group.

The most thorough work indicating a relationship between fluorine intake, mottled teeth, and caries is that of Dean and his associates. One survey (8) showed that the occurrence of caries in nine year old children in selected cities of Kansas, Colorado, and Illinois was lower for both the deciduous and permanent teeth in mottled enamel areas than was the case in other places. Only 4 per cent of the children using water supplies containing 0.6 to 1.5 p.p.m. of fluorine were

only when fluorine was present with the casein indicated that fluorine was the effective principle. Other investigators, Miller (18), Cox *et al* (20), Cheyne (21) and Sognnaes (22), have indicated that fluorine greatly reduces the amount of caries produced by coarse particle diets.

There are two reasons why only guarded conclusions should be drawn from the above findings. In the first place, the coarse particle caries of rats resembles human caries only so far as the destruction of dentin is concerned and is probably primarily the result of fracture of the teeth (23). It is even possible, therefore, that fluorine may influence rat caries as a result of toxic changes brought about in the nerves or muscles related to the jaws and consequently its limitation would not be related to any known factors in human caries. In the second place, the intake of fluorine necessary to produce changes in the caries incidence in rats is far in excess of that which modifies human caries. This, of course, may be the result of a greater fluorine resistance in the case of the rats.

The evidence just cited from the three fields of investigation indicates that fluorine is an agent which has a remarkable effect on dental caries. The findings in the field studies are particularly convincing and, even were they not supported as they are, by the results of chemical analyses and animal experiments, they are striking enough to suggest that, if the mechanism by which fluorine enhances the caries resistance could be ascertained, it might lead to a practical method for the prevention of dental decay. The succeeding section of this paper attempts to interpret studies which have been carried out to determine the mechanism of fluorine action.

## II. MECHANISM OF FLUORINE ACTION

It is axiomatic that in preventing dental caries fluorine must act either by weakening the attacking forces which cause a breakdown of the teeth or by enhancing the power of the teeth to withstand this attack. Since almost all responsible authorities agree that the initial lesion of dental caries is a decalcification of the enamel by acids produced by bacterial fermentation of food, fluorine must act either by reducing the formation of acids or by making the enamel and dentin more resistant to their action. It is further believed that the balance

as further evidence that the incorporation of fluorine in the teeth during calcification is not the factor which determines the resistance to caries. It also seems to indicate that the effect is not dependent upon a continuous washing of the teeth with fluorine-containing saliva, otherwise we would expect the upper anterior teeth to be less adequately protected than the molars.

### *Chemical Analyses of the Teeth*

The many chemical analyses of the teeth have as a whole failed to reveal differences between carious and non-carious teeth. The principal exception to this is found in fluorine analyses. In 1899 Hempel and Scheffler (13) reported that non-carious teeth contained more fluorine than carious teeth. The value of their results is limited by the fact that they employed small amounts of material containing unknown proportions of enamel and dentin and because the then available methods of fluorine analysis were of questionable accuracy (14). Recently, however, modern methods of fluorine analysis have been applied to separated enamel and dentin. Armstrong and Brekhus (15) have shown that the fluorine content of the enamel of non-carious teeth contains 0.0111 per cent of fluorine, whereas that of carious teeth only 0.0069 per cent. These differences, according to the authors, are statistically significant. Similar differences were not found in the fluorine content of carious and non-carious dentin.

### *Experimental Caries in Rats*

While there is serious doubt as to how closely the lesions produced in the molar teeth of rats by feeding coarse particles of corn or rice resemble human caries, this condition remains the closest counterpart of human caries that can be produced at will in experimental animals. Consequently, it has been used extensively in attempts to indicate the significance of various dietary deficiencies or supplements upon the occurrence of dental caries. Using this experimental procedure, Lilly (16) observed the reduction of "caries" from 60 per cent to 10.3 per cent when casein was added to a caries-producing diet. The subsequent demonstration by Hodge, Luce-Clausen and Brown (17) that commercial casein was heavily contaminated with fluorine and the demonstration (19) that the reduction of caries was brought about

blood of cats ever reaches the saliva. This is true in spite of the tremendously high concentration of fluorine in the blood which vastly exceeds that ever found in natural condition. The bulk of the fluorine passes to the urine or is found in the bones (27).

### *The Formation of Acids*

The action of salivary amylase in breaking down starches to more readily fermentable sugars may be considered to be the first step in the formation of acids from food carbohydrates. While evidence of a slight inhibition of amylase activity by fluorides has been reported (28, 29, 30), the more convincing investigations of McClure (31) showed no such effect. McClure found that the addition of from 0.76 to 760 p.p.m. of fluorine to the saliva did not affect its enzymatic activity and that there was no difference in the amylolytic activity between the salivas of children drinking water containing 1.8 p.p.m. of fluorine and those using fluorine-free waters.

The action of bacteria in fermentation could be weakened either by reducing the bacterial population or interfering with the activity of the organisms regardless of their numbers. Experiments directed towards exploring this first possibility have not given definite results. Bunting *et al.* (6) investigated the bacterial flora of children of Minark, Illinois who were receiving a fluorine-containing drinking water. They concluded that "bacterial cultures taken from the group did not show correlations with the activities of dental caries as is found in other communities." So far as can be seen from their results, the deviations which normally occur are not in any one direction. More recently, a comparison was made (10) of the occurrence of *L. acidophilus* in children using a low (Quincy, Illinois) and a high fluorine (Galesburg, Illinois) drinking water. It was found that 52 per cent of the former children had acidophilus counts of 30 thousand or over, while only 15 per cent of the latter had counts of this magnitude. Harrison (32) showed that in rats receiving fluorine only 1 per cent of the oral flora was lactobacilli as compared with 18 per cent in those receiving no fluorine. The streptococcal count was not affected similarly. The significance of these findings is doubtful because the reduced lactobacilli counts are probably the result of the observed reduction in the numbers of cavities in the fluorine groups. Any conclusions

between the attack and the resistance may be swung in either direction by the action of the saliva. In keeping with this analysis of the process of caries, the most logical method of examining the mechanism of fluorine action is to consider separately the factors of 1) salivary action, 2) acid formation, and 3) tooth resistance to see the manner in which each of them is affected.

### *The Action of Saliva*

Since the manner in which saliva influences the progress of dental caries is not known, the only method of testing whether it is an important link in the mechanism of fluorine action is to determine whether the effects of fluorine are still shown in its absence. To this end, Cheyne (21) carried out tests on the effect of fluorine on experimental caries in rats from which the salivary glands had been extirpated. It was found that in the absence of oral secretions there was a great increase in the amount of caries but that when fluorine was administered the amount of tooth destruction was reduced to one-fifth. On the other hand, when desalivated animals which had previously been fed quantities of fluorine sufficient to cause mottling of the teeth (and presumably an increased fluorine-content in the enamel) were placed on the caries-producing diet, no significant reduction of caries occurred (24). This seems to indicate that the continuous action of fluorine is required to reduce caries activity, but that the fluorine occurring in the saliva is not important in this matter. A different mechanism is suggested, however, by Cox's (20) finding of a reduction of caries in the offspring of animals fed a high fluorine diet regardless of its absence in their own diet. The conclusion that the saliva is unimportant is in keeping with observations made in human field studies. These have shown (10) that the upper anterior teeth which show the greatest resistance to caries are not the teeth which have the benefit of continuous flushing by the saliva, and that the fluorine content of the salivas of children with caries immunity resulting from a fluoride-containing water supply does not differ from that of children on a pure water supply (25). Another reason for believing that the secretion of fluorine in the saliva is not important in caries prevention is the demonstration (26), by use of radioactive isotopes, that only about 0.1 per cent of the fluorine injected into the

blood or cats ever reaches the saliva. This is true in spite of the tremendously high concentration of fluorine in the blood which vastly exceeds that ever found in natural condition. The bulk of the fluorine passes to the urine or is found in the bones (27).

### *The Formation of Acids*

The action of salivary amylase in breaking down starches to more readily fermentable sugars may be considered to be the first step in the formation of acids from food carbohydrates. While evidence of a slight inhibition of amylase activity by fluorides has been reported (28, 29, 30), the more convincing investigations of McClure (31) showed no such effect. McClure found that the addition of from 0.76 to 760 p.p.m. of fluorine to the saliva did not affect its enzymatic activity and that there was no difference in the amylolytic activity between the salivas of children drinking water containing 1.8 p.p.m. of fluorine and those using fluorine-free waters.

The action of bacteria in fermentation could be weakened either by reducing the bacterial population or interfering with the activity of the organisms regardless of their numbers. Experiments directed towards exploring this first possibility have not given definite results. Bunting *et al.* (6) investigated the bacterial flora of children of Minark, Illinois who were receiving a fluorine-containing drinking water. They concluded that 'bacterial cultures taken from the group did not show correlations with the activities of dental caries as is found in other communities'. So far as can be seen from their results, the deviations which normally occur are not in any one direction. More recently, a comparison was made (10) of the occurrence of *L. acidophilus* in children using a low (Quincy, Illinois) and a high fluorine (Galesburg, Illinois) drinking water. It was found that 52 per cent of the former children had acidophilus counts of 30 thousand or over, while only 15 per cent of the latter had counts of this magnitude. Harrison (32) showed that in rats receiving fluorine only 1 per cent of the oral flora was lactobacilli as compared with 18 per cent in those receiving no fluorine. The streptococcal count was not affected similarly. The significance of these findings is doubtful because the reduced lactobacilli counts are probably the result of the observed reduction in the numbers of cavities in the fluorine groups. Any conclusions



drawn are also weakened by the failure in the human studies to consider adequately acidogenic organisms other than lactobacilli

The other possibility that fluorine might affect acid production in the mouth by limiting the action of bacteria rather than by reducing their numbers has been investigated by Bibby and Van Kesteren (33). By comparing the bacterial counts and the acid production of various types of mouth organisms, they established growth curves and acid-production curves. It was found that concentrations of only two parts per million of sodium fluoride reduced the rate of acid production and that this effect increased proportionally with the increase in concentrations of fluoride. In spite of the marked effects on acid production, the rate of multiplication of the organisms was not influenced until fluorine concentrations (250 to 500 p p m) far beyond those which occur in the mouth were reached. It was observed that dental tissues obtained from rats fed high fluorine diets also reduced the amounts of acid produced by oral micro-organisms and that enamel and dentin on which fluorine had been adsorbed by brief exposure to fluoride solutions manifested a similar inhibitory effect.

While the above results seem very significant, it should be pointed out that most of the effects were observed in systems where fluorides were constantly present and consequently cannot be applied exactly to the conditions found in the human mouth, that is, unless the saliva were continually resecreted the fluorine in concentrations equal to that found in the drinking water. Preliminary analytical evidence (25, 26, 27) shows that this is far from being the case. Clinical findings already discussed also indicate that the effects of fluorine manifest themselves independently of the saliva. Although it seems improbable that drinking water which is in contact with the mouth organisms for so short a period of time could bring about effects on bacteria similar to those noted experimentally, the finding that fluorosed teeth or fluoride-treated enamel and dentine do inhibit acid production indicates a manner by which fluorine may continuously prevent acid production on the tooth surfaces. Miller (18) has suggested that fluorine may be concentrated in the bacterial plaque on the outside of the teeth, thus preventing acid production at that site. As yet, however, there is no direct evidence to show that this does

occur and since fluorine combination with the tooth itself provides an equally sound explanation, it seems likely that the effects observed by Miller could have been brought about in the latter way.

### *Tooth Resistance*

Two mechanisms can be postulated by which fluorine might add to tooth resistance. One is that it may act in some way to increase the ability of the tooth to repair or replace enamel and dentin which are being destroyed by caries, the other is that it adds to the power of the tooth passively to resist the process of caries.

There is no evidence to suggest that the former or vital type of reaction is augmented in any way other than a few as yet unconfirmed suggestions by Finn and Morgareidge (34) that fluorine is necessary for optimal phosphorus metabolism. (The possibility that a vital response of the saliva may aid in the repair of caries has to be kept in mind, but discussion of that possibility is not in place here.) The latter possibility is supported by a variety of evidence.

While actual experiments with enamel and dentin first led to the conclusion that fluorine added to the acid resistance of enamel, it is convenient to consider findings from other fields first. In work relating to the utilization of rock phosphates as fertilizers, MacIntire, Harden, Oldham and Hammond (35) have indicated that the solubility of basic calcium phosphates, which have the same chemical composition as inorganic tooth substance (36), is determined by the fluorine content. Similarly Jacobs Hill, Marshall and Reynolds (37) have shown that calcium phosphates containing appreciable amounts of fluorine have a reduced citric acid solubility. The analogy to the situation which occurs in dental caries is obvious. Volker (38) found that the teeth with a high fluorine content obtained from rats fed a fluorine-rich diet were more resistant to the action of acid than those obtained from animals on a fluorine-free diet. Likewise the addition of fluorosed tooth substances to bacterial cultures caused a reduction in acid production. The above findings indicate that increased amounts of fluorine in the teeth will increase their resistance to acid and hence to dental caries, a finding in keeping with clinical observations and Armstrong's demonstration of a high fluorine-content in

the enamel of caries-resistant teeth. Consequently, it is cogent to consider the mechanisms which may influence the amount of fluorine in the teeth.

There are at least three possible ways by which fluorine may reach the dental hard tissues. These are 1) the incorporation of the element during the period of tooth formation, 2) the continuous deposit and consequent increment of fluorine in fully formed teeth as a result of its passage through the blood stream and pulp to the dentin and enamel, 3) a combination of the enamel with fluorine brought in contact with the external surfaces of the teeth in saliva, drinking water, or food.

The finding of higher fluorine contents in the teeth with mottled enamel (39, 40) resulting from a high fluorine content in the drinking water, and the finding of a high fluorine content on the teeth of populations ingesting much fluorine in their food (41) indicate that the content of fluorine in the teeth is dependent upon the amount ingested during the period of tooth calcification. Animal experiments also offer evidence to support this point. Krick *et al* (42), Munoz (43), McClure (44), and others have shown a marked increase in the fluorine content of that portion of the rat incisor formed during periods of high fluorine intake. That both the enamel and dentin are affected was demonstrated by Hodge *et al* (17) who found marked increases in fluorine in both tissues when rats were fed an excessively high fluorine diet. Analyses by Bowes and Murry (40) and Armstrong and Brekhus (39) gave higher than normal fluorine values in both fluorosed human enamel and dentin. While the values of the two groups of workers are not the same, they reveal a relatively greater increase in the dentin than in the enamel. It should be noted, however, that in none of this work is there absolute proof that the high fluorine content could not be accounted for, at least in part, by a continued increase in the amount of fluorine in the fully formed tooth. It should also be borne in mind that we are concerned particularly with the fluorine content of teeth in relation to caries resistance rather than mottling and that, since the caries-preventing action of fluorine is equally as effective in non-mottled teeth, the foregoing observations on mottled teeth do not necessarily apply to the problem. Several observations on teeth rendered caries-resistant by fluorine indicate

that this resistance may be independent of fluorine deposited during tooth formation. Deciduous teeth which are protected from the effects of fluorine during formation and consequently do not show mottling, are nevertheless protected from caries (3). Bunting *et al* (6) have noted that children moving into areas with a high fluorine content in the drinking water after the age of ten when the most susceptible teeth have been formed, have a resistance to caries equal to those using the water throughout life. Dean (12) has made similar observations. Evidence of a different sort appears in Cheyne's (24) finding that fluorosed rat molars have no added resistance to experimental caries after the ration of fluorine is suspended. The possibility that the caries resistance of non-mottled teeth is dependent upon a post eruptive increase of fluorine is suggested by Armstrong's (15) finding that, unlike the dentin of mottled teeth, the dentin of caries-resistant teeth had no more than the normal amount of fluorine, whereas the content of the enamel which could combine directly with fluorine from the water or food is increased.

The possibility that fluorine can be added to the tooth from within depends upon the existence of metabolic processes in the fully calcified tooth. Early attempts to demonstrate such activities by means of staining and diffusion experiments gave inconclusive results because only extracted teeth could be used for such tests and the methods employed did not give quantitative results. The use of radioactive isotopes of such elements as phosphorus has made it possible to obtain much more adequate information on the mineral metabolism of the teeth. Using radioactive phosphorus P-32, Hevesy, Holst and Krogh (45), and later LeFevre and Bale (46), have shown that, when this isotope is fed in the diet, it is deposited in the dentin of fully erupted teeth. Armstrong (47) has made similar observations in adult cats and finds that the marked phosphorus reaching the enamel is 6.7 to 10 per cent of that occurring in the dentin. Volker and Sognnaes (48) have confirmed these findings. They have also shown (48) that the phosphorus exchange in the outer part of the enamel is greater than that in the inner portion. While it cannot be assumed that fluorine would be carried into the dentin and enamel in the same way as phosphorus, similar experimental procedures are needed to establish the extent to which fluorine is added to the fully formed tooth. In-

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almost complete substitution of all the hydroxyl ions of bone by fluorine to give a fluorapatite. This has been suggested as the mechanism which accounts for the extremely high fluoride content of fossilized bones. The rapidity of the reaction between fluoride and bone is indicated by the effectiveness of filters of powdered bone in removing excess fluorine from drinking water as demonstrated by Smith and Smith (53). Hydroxylapatite and calcium phosphates have also been shown to combine actively with fluorides by MacIntyre and Hammond (54) and Adler, Klein and Lindsay (55), respectively. Previous researches have shown that the basic inorganic molecules of tooth, bone and phosphate rocks are essentially the same (36). This suggests that fluorides would react with enamel and dentin in the same way that they do with the other basic calcium phosphates. Such a reaction has been demonstrated by Volker (56) who, using reduction in acid solubility as an indication of the fluorine combination, found up to 50 per cent reduction in the solubilities of enamel and dentin after a few minutes treatment with sodium, potassium, ammonium or calcium fluoride solutions. The change produced in the dental tissues seemed to be a permanent one as would be expected in view of the fossilization of bone. By using radioactive fluorine, Volker, Hodge, Wilson, and Van Voohhis (57) demonstrated that the combination of fluorine with tooth substance obeyed Freundlich's equation for a true absorption. This finding does not necessarily rule out the possibility suggested by Ercoli (58) that the fluoride ions replace the phosphate ions in the calcium phosphates. It is interesting to note that enamel and dentin treated with fluoride solutions were more resistant not only to destruction by organic acids (56) but also to destruction by bacterial cultures (59). Apparently, sufficient fluorine was taken up to exert definitely inhibited effects on the bacterial metabolism.

The rapidity with which fluorine combines with bone, as indicated by the effectiveness of the bone filter in removing fluorides from running water (53) and the speed of its reaction with enamel and dentin as demonstrated in Volker's tests (56), suggest that the fluorine of drinking water may combine directly with the enamel of the teeth while the water is in contact with the teeth. This possibility receives support in the observation that the effects of fluorine in the

direct evidence that fluorine does pass into the dentin is found in Sognnaes' (22) experiments with rat caries. He found that desalivated rats fed fluorine by a stomach tube showed less destruction of the dentin than those not receiving such treatment and inferred that this indicated an augmented resistance of the dentin brought about by fluorine conveyed into the dentin by way of the blood stream. McClure (44) has shown that the bones contain much more fluorine than the teeth and believes that fluorine fed in the diet is first deposited in the bones. Our (27) experiments with radioactive fluorine have confirmed this and show that per gram of tissue the uptake of fluorine in the bone is approximately three times that of the fully formed teeth. Consequently, to add to the fluorine content of the teeth post-eruptively, it would be necessary to bring about a great increase in the bone fluoride.

In view of Armstrong's (15) finding that the enamel of caries resistant teeth contained increased amounts of fluorine while the dentin did not, the possibility that fluorine may be added to the tooth by contact with fluoride-containing solutions deserves consideration. Fluorine in the saliva or water could combine with the enamel or dentin either if there were the passage of inorganic ions into the tooth from the outside or if the fluorine had a special affinity for tooth substance resulting in adsorption or chemical combination. While clinical observations have led Andresen (49) and others to suggest that enamel is "remineralized," there is no satisfactory experimental evidence to show that enamel does take up inorganic elements from its environment. The only positive evidence of this is Volker and Sognnaes' demonstration (48) that radioactive phosphorus appears in greater concentrations on the enamel surface than in the middle layers of the enamel. Additional support for this belief may be found in the P 32 adsorption studies of LeFevre and Levy (50) and Armstrong (51).

The possibility that fluorine has a special affinity for tooth substance rests upon another foundation. The active combination of bone with fluorine was demonstrated by Carnot (52) who found that bone exposed to dilute fluoride solution for five months showed an increase in fluorine content from 31 parts per 100 to 474 parts per 100. It is interesting to note that theoretically this represents an

Attempts to alter caries resistance by continuous ingestion of small doses of fluorine are subject to all the difficulties of establishing safe and effective fluorine dosage. More important than this, however, is the fact that as yet there is no justifiable theoretical background to suggest that such a procedure might reduce dental caries. There is no evidence to indicate that the destructibility of the formed tooth can be significantly changed to suggest that the mineral metabolism might influence tooth resistance by way of the blood stream and the pulp or through the saliva.

An approach towards caries control by changing tooth resistance and incidentally weakening the attacking processes of caries by the use of local applications of fluoride to the fully formed tooth seems to offer the greatest hope of providing a practical method. Such a procedure could avoid the possible complications resulting from ingestion of the fluorides, either by having treatments with relatively strong fluoride solutions carried out by dentists as part of the procedure of dental prophylaxis or by using weak solutions as mouth washes or denturices. While until now it has lacked scientific reason, the latter idea is not new. Before the turn of the century Denniger (63) advocated the use of, and had a patent on, fluorine-containing denturices. Recently, Atkins (64) has employed a solution of 5 p p m of sodium fluoride as a denturice. The effectiveness of such procedures has not yet been established, and merits an extensive trial under well controlled clinical conditions.

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prevention of dental caries are most marked in the upper anterior teeth which have the greatest contact with drinking water. The increase of fluorine in enamel but not dentin of caries-resistant teeth further bears it out. The demonstration of an increased fluorine content of the enamel of anterior teeth as compared with posterior teeth without corresponding increases of the dentin would fairly conclusively establish direct combination with fluorine as the mechanism by which tooth fluorine and tooth resistance are increased. Studies with experimental rat caries further indicate this possibility. It was indicated by Cheyne's finding (21) of a caries reduction in desalivated rats, the teeth of which were formed before the fluorine supplements were added. Sognnaes (22) obtained preliminary evidence that applications of fluorides to rat molars, under conditions which prevented its ingestion, retarded the progress of caries.

### III POSSIBLE THERAPEUTIC USE OF FLUORINE IN DENTAL CARIES

The above considerations naturally lead to the question of the possibility of using some type of fluorine therapy as a means of preventing dental caries. That this might be accomplished, by the incorporation of fluorine into the tooth during calcification, was suggested as long ago as 1892 by Crichton-Brown (60). However, in the discussion of the mode of action of fluorine, it has already been pointed out that resistance to caries does not seem to depend upon the laying down of fluorine in the forming tooth. Even if this were the case, it would be difficult to work out a practical method for significantly raising the fluorine content of the teeth. First, it is very doubtful whether effective amounts of fluorine can be transferred across the placenta or in the maternal milk to reach the calcifying deciduous teeth. Second, there is the possibility, particularly as far as the permanent teeth are concerned, that any attempt of this sort might result in unsightly mottling of the enamel. While the addition of optimal quantities of fluorine to the water (Cox) (61) appears simple, variable conditions in different localities, different water compositions, the effects of food cooking (62), and as yet unknown influences of other water constituents would all have to be controlled to make such a procedure practicable and safe. Kindred problems appear in any attempts to administer fluorine by other methods such as by capsules or in the food.

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## FAVISM

### A SINGULAR DISEASE CHIEFLY AFFECTING THE RED BLOOD CELLS

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#### HISTORY

Favism is certainly a very old condition. The writings of antiquity contain frequent allusions to the manifestations and prevalence of this illness. The first definite reports go back earlier than the 5th century B C. Historical research (4, 40, 75) leads to the conclusion that it formerly had a very wide distribution in the Mediterranean Basin. The first really scientific studies of this condition were begun, however, in 1856 (52). Since that time about 100 contributions have appeared in the Italian literature and a few others in the French, English, German and American literature. The complexity of the pathogenesis explains why until now no complete agreement has been reached as to the mechanism of the disease. Great interest attaches to the condition, on one hand due to its possible bearing upon other hemolytic anemias of more common occurrence, on the other hand due to the description of some cases in the United States.

#### DEFINITION

The term favism is attributed to a clinical syndrome caused either by ingestion of the seeds, or by inhalation of the principles originated in the flowers of *Vicia Faba* (commonly known as broad bean)<sup>2</sup>. The clinical picture is characterized chiefly by the sudden appearance of a hemolytic attack, followed by hemoglobinuria, jaundice, and vascular symptoms.

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<sup>2</sup> Strictly speaking the term "favism" is improper, because ordinarily the suffix "ism" connotes a well-defined poisoning (morphinism, tabagism, alcoholism). Cause of the symptoms is here more complex.



personal observation (59) of a few cases of favism occurring in Sardinia, but in patients born on the mainland and without Sardinian ancestry is, however, contrary to this view

2 *Family* Quite frequently many cases occur among the members of the same family, as Macciotta (64), Piana (91), Auricchio (4), McCrae and Ullery (77) observed. In some families under my observation (59) all members had suffered from favism at one time or another

3 *Environment* The environment has a definite relation to one of the chief clinical syndromes of favism, namely that caused by inhalation. Large fields in which the fava beans are cultivated constitute the usual surroundings in which the attacks take place, probably because the pollen is of a very sticky type and has no wide dissemination. On the other hand, attacks caused by ingestion may occur anywhere, being, however, more frequent where the custom of eating this vegetable frequently is most wide spread. Moreover extensive areas of its cultivation may be important for the development of the sensitization, to be discussed below

4 *Season* Attacks of favism caused by inhalation occur chiefly during the months of April and May<sup>4</sup> when the plants blossom. Attacks of favism caused by ingestion may occur in any month. Most of them, however, occur between May and August, when the seeds are fresh. In later months of the year rare cases occur, usually showing a milder symptomatology, which are apparently caused by the ingestion of the dried seeds

5 *The plant* The plant *Vicia faba* (called in Italian and Portuguese "fava," known in English as the "horse bean," "broad bean," or "fava bean") is undoubtedly the cause of the attacks.<sup>5</sup> Some authors (2, 31, 32, 69) are of the opinion that a particular toxicity of the Sardinian plant is responsible for the frequency of the disease in that region. Two facts, however, disprove this hypothesis (a) Patients born and brought up in Sardinia may be subject to attacks

<sup>4</sup> I am referring here to the period of blossoming of the plant in Sardinia. It is possible that in other countries there is a slight displacement of this period. Moreover, as Parlato (132) states, late blossoming of some flowers occurs

<sup>5</sup> The different names are applied to different varieties of the plant. Fava bean should be preferred, and applied to fruits causing the disease.

## DISTRIBUTION

The disease is chiefly present among the inhabitants of the Italian island of Sardinia, where many thousands of cases occur every year. With less frequency it is evident in Sicily (mainly in the district of Messina), and, on the mainland, in some districts of Calabria. Isolated cases have been described in continental Italy, in the Greek islands, and in North Africa. Up to the present only three cases have been reported in the United States (McCrae and Ullery (77), Hutton (49), Campagna)<sup>3</sup>. I believe however, that in the United States more cases will be recognized in the future, for the following reasons:

- 1 A large Mediterranean population lives in certain parts of the United States
- 2 Fava beans are cultivated extensively in some States (mainly New York, New Jersey, Illinois, California)
- 3 They are a staple article of diet in the United States, being even imported as canned food from Italy

Therefore many of the factors necessary for the occurrence of this disease are present.

## GENERAL CLINICAL ASPECTS

1 *Race* Some authors are of the opinion that a racial factor may explain the definite prevalence of the disease on the island of Sardinia. The local population, numbering about one million, possesses different racial characteristics from those of the people inhabiting the mainland. These Sardinians (as well as some smaller groups in Sicily and Calabria) seem to have kept the more typical characteristics of the original Mediterranean race. It has been suggested that this fact would tend to account for the present localization of the disease which was so much more diffused in the past.

Confirmation of this racial theory has seemingly been attained by the observation that most of the rare cases of favism noted in continental Italy have occurred in patients of Sardinian extraction. My

<sup>3</sup> The case of Dr. T. V. Campagna of Boston (personal communication) is of particular interest, as the patient, a woman of Sicilian descent, had the first attack in Massachusetts.

personal observation (59) of a few cases of favism occurring in Sardinia, but in patients born on the mainland and without Sardinian ancestry is, however, contrary to this view.

2. *Family*. Quite frequently many cases occur among the members of the same family, as Macciotta (64), Piana (91), Auricchio (4) McCrae and Ullery (77) observed. In some families under my observation (59) all members had suffered from favism at one time or another.

3. *Environment*. The environment has a definite relation to one of the chief clinical syndromes of favism, namely that caused by inhalation. Large fields in which the fava beans are cultivated constitute the usual surroundings in which the attacks take place, probably because the pollen is of a very sticky type and has no wide dissemination. On the other hand, attacks caused by ingestion may occur anywhere being, however, more frequent where the custom of eating this vegetable frequently is most wide spread. Moreover extensive areas of its cultivation may be important for the development of the sensitization, to be discussed below.

4. *Season*. Attacks of favism caused by inhalation occur chiefly during the months of April and May<sup>4</sup> when the plants blossom. Attacks of favism caused by ingestion may occur in any month. Most of them, however, occur between May and August, when the seeds are fresh. In later months of the year rare cases occur, usually showing a milder symptomatology, which are apparently caused by the ingestion of the dried seeds.

5. *The plant*. The plant *Vicia faba* (called in Italian and Portuguese fava," known in English as the 'horse bean,' 'broad bean,' or 'fava bean') is undoubtedly the cause of the attacks.<sup>5</sup> Some authors (2, 31, 32, 69) are of the opinion that a particular toxicity of the Sardinian plant is responsible for the frequency of the disease in that region. Two facts, however, disprove this hypothesis: (a) Patients born and brought up in Sardinia may be subject to attacks

<sup>4</sup> I am referring here to the period of blossoming of the plant in Sardinia. It is possible that in other countries there is a slight displacement of this period. Moreover, as Parnis (132) states, late blossoming of some flowers occurs.

<sup>5</sup> The different names are applied to different varieties of the plant. Fava bean should be preferred, and applied to events causing the disease.



in any country, upon ingestion of seeds of local cultivation, (b) Extracts of foreign seeds produce in Sardinian patients exactly the same skin reactions as those of the native seeds. My researches (59) have shown that the leaves contain some of the active principle, and that exceptionally they also may cause clinical symptoms. It is interesting to note that no correlation exists between the amount of the active principle ingested and the severity of the attacks.

6 *Parasites* By analogy with other clinical syndromes Lusena (68) has suggested that parasites of the fava beans may be responsible for the disease. The researches of my associates and myself (58, 59, 60, 86, 87, 88, 89), however, deny this possibility. Certain parasites are often present on leaves, others very inconstantly on fresh seeds, and others very often on dried seeds. The extracts of the parasites of dried seeds show some activity as allergens, if tried on the skin of patients, but this does not seem very important in the pathogenesis of the disease, as will be explained later.

An extensive toxicologic study on all parasites of the plant was accomplished by Tocco (100) with no conclusive evidence presented as to their rôle in favism.

#### CLINICAL FEATURES OF THE ATTACKS

Two chief types of attacks may be observed: (1) that caused by inhalation, (2) that caused by ingestion. The former occurs when the patient inhales the pollen of the flowers, and more rarely when he inhales the emanation of the leaves or that of the seeds during or after cooking.

Inhalation of the active principle (probably pollen) occurs during a walk in, or near, the fields where the plants are cultivated, when they are in bloom. The small amount of pollen liberated, its high specific gravity, and its sticky quality may account for the rare occurrence of attacks caused by inhalation within the towns, even during the blooming season.

The attack caused by ingestion occurs chiefly after eating either raw pods or raw fresh seeds. It may be due to ingestion of fresh seeds incompletely cooked (either broiled or fried), and more rarely to cooked dried seeds. Sometimes intake of a very small amount of fava proteins is sufficient to bring about an attack.

I recall one case in a child of 5 years under my personal supervision, in which the history showed that intake of a single seed was sufficient to provoke the characteristic syndrome. Another interesting example of the above is brought to mind in another of my cases in which simply drinking water from a container in which fava leaves had been kept for some time resulted in the occurrence of typical manifestations. This patient illustrated another curious possibility, in that ingestion of goat's milk, after the goat had been fed fava beans, produced a typical attack. Milk obtained from the same goat fed the usual goat's fare (which, of course precluded fava beans) was absolutely devoid of any pathogenic property.

Of 1211 cases, reported by Fermi (35), 38 percent of the attacks were caused by inhalation, and 62 percent by ingestion. As both types of attack show similar symptoms, they can be described together.

*Early stage* The first symptoms may appear a few seconds after *inhalation* of principles originated in the flowers or plant of the fava bean. Usually, however, they occur later the time element varying from a few minutes to some hours. After *ingestion* of fava beans there is a longer delay from 5 to 24 hours.

In the sudden attacks, chiefly caused by inhalation the first symptoms are those of a dizzy spell, sometimes reaching the stage of a collapse. More usually malaise, headache, dizziness and nausea appear gradually. Then repeated yawnings, vomiting, chill, pallor, pain in the lumbar region are followed by a marked rise of the temperature.

*The attack* Later the more specific symptoms appear, and are characterized by two chief features hemoglobinuria and icterus. The succession of signs may vary as to the time of onset. Appearance of hemoglobinuria occurs between 5 and 30 hours, the shorter period being associated with the inhalation the longer with the ingestion attacks. The urine shows then a change in color varying from red to black. After a few hours the jaundice appears and reaches a very intense stage. It is accompanied by an enlargement of the liver and spleen. The heart is dilated, and functional murmurs become evident. The fever is inconstant and irregular. It reaches 101-103° in the first day then either becomes remittent or intermittent, some-

in any country, upon ingestion of seeds of local cultivation, (b) Extracts of foreign seeds produce in Sardinian patients exactly the same skin reactions as those of the native seeds. My researches (59) have shown that the leaves contain some of the active principle, and that exceptionally they also may cause clinical symptoms. It is interesting to note that no correlation exists between the amount of the active principle ingested and the severity of the attacks.

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75) The smears show anisocytosis early occurrence of many reticulated cells (30 to 60 per cent) polychromatophilic cells, and erythroblasts. Some red cells with basophilic granules may be seen also, as well as hemocytoblasts

The red blood cell resistance to saline solutions may be slightly diminished at the beginning of the attack according to Macciotta (64) Manai (75), and MacCrae and Ullery (77), but later is usually normal or even increased, according to Gasbarrini (40), and Manai (75)

There is a marked leucocytosis during the first 6 to 7 days. This occurs chiefly in children in whom it reaches the figure of 10 000 to 40 000 per cubic millimeter. The leucocytosis subsides with the end of the hemoglobinuria according to Filia (37), Macciotta (64), Auricchio (4) and Chieffi (20). Manai (75) found in the differential count three successive stages. (a) slight increase in the neutrophiles; (b) increase in the lymphocytes, sometimes accompanied by mononucleosis often by eosinophilia, (c) normal percentage of neutrophiles and lymphocytes but often mononucleosis and eosinophilia. The author does not state the exact time relationship between the three phases but it may be deduced from his records that they follow each other within 5 to 8 days

The blood platelets were found increased during the attack by Manai (75). MacCrae and Ullery (77) found reduction of the platelets at the beginning an increase later in the attack

*The urine.* Often only a few hours after the beginning of the attack the urine contains a large amount of hemoglobin which continues to be present for 1 to 3 days. If the hemolytic process lasts longer the patient usually dies. Consequently according to Manai (75) a more prolonged hemoglobinuria is never observed. Spectroscopic studies show the presence of oxymoglobin and also methemoglobin the percentage of which ranges between 0.05 and 0.9 percent (Zoia (105) Gasbarrini (40)). During and after the hemoglobinuria a large amount of urobilin may be found in the urine. Biliary salts, on the contrary, are always absent.

Albuminuria from 0.01 to 0.2 percent is frequently present during the attack. The urine shows an upper layer containing the pig-

times simulating the fever of a malarial attack. Cases resulting in fatality show either a sudden rise or a sudden drop of the temperature just prior to death. The skin of the patient is not only yellow, due to the jaundice, but extremely pale, assuming therefore a typical pale-green color. Itching and bradycardia are absent.

*Course of the attack* The typical attack has a duration of 2 to 6 days. In fatal cases, more frequently children, death occurs within the first 2 days, rarely during the 3rd day. When the patient recovers, hemoglobinuria and fever terminate after the 5th to 6th day. The jaundice lasts longer and is followed by anemia, which sometimes is quickly compensated, but in other instances is still present after one month.

*Blood picture* Many studies have been undertaken of the blood picture during and after the attack, in order to clarify its cause and mechanism. It seems that the phase of hemoglobinemia is very transient, as only Biddau (16) has been able, quite recently, to detect the occurrence of hemoglobin in the plasma<sup>6</sup>. During the jaundice phase, the color of the serum is greenish-yellow, owing to the presence of bilirubin. The proteic quotient was found by Macciotta (64, 65) to be inverted. The coagulation time, bleeding time, and coagulum retractility were found to be normal by Manai (75). The blood calcium and magnesium values were found to be lowered or normal, blood glucose was sometimes increased (70, 75). The blood uric acid was found to be lowered (70, 75). The blood potassium may be even tripled during the attack, in contrast with a lowering of sodium by as much as one-half of the normal value (70, 75). The blood serum obtained during an attack and mixed *in vitro* either with normal red blood cells or with the red blood cells of the patient does not cause hemolysis. The Donath-Landsteiner test was found to be negative by Gasbarrini (40), MacCrae and Ullery (77), and Hutton (49), in spite of a contrary report by Frongia (38). Cholesterol is low in the blood according to Gianì (44). During the attack the number of red blood cells diminishes, so that the count often is less than 1 million, but more usually from 1 to 2 million per cubic millimeter. Some authors claim that the color index is frequently lowered (72,

<sup>6</sup> New studies with improved technique should be done in order to clarify this point.

## POST-MORTEM EXAMINATION

Autopsy reports of only three cases have been published up to now by Gasbarrini (40) Lunghetti (67) and Guccione (48). The chief lesions observed were the following.

1. Either a status lymphaticus (Guccione), or chronic lesions of the liver and spleen (Gasbarrini), or a multiple visceral sclerosis (Lunghetti)
2. Some degenerative lesions of the nervous centers, of the kidneys, and of the liver
3. Acute inflammation of the gastro-intestinal tract and of the bronchi.
4. Intense reaction of the reticulo-endothelial system and normo-megaloblastic hyperplasia of the bone marrow
5. Acute swelling of the spleen, accumulation of white cells in the capillaries of many organs, perivascular lymphocytic infiltrates, venous thrombi.

Guccione (48) finds many analogies between the last two groups of lesions, which seem more connected with favism, and those found in patients dead after malarial or quinine hemoglobinuria, as described by Ziemann (144), as well as in animals which have died as a result of experimental anaphylaxis (Cesaris Demel (113)).

## PATHOGENESIS

Three theories have been advanced for explaining favism: the infectious or parasitic, the toxic, and the allergic theory.

## INFECTIOUS OR PARASITIC THEORY

This concept was advocated by Cipriani (22, 23), who suggested the possibility of some *bacterium* acting either when the plant blossomed, or when the seed was still quite immature. De Semo (23) quotes some botanists as attributing favism to a *fungus* living in the seed of fava beans. Grande (47) believed that he had succeeded in isolating a *bacillus* from the urine of a case of favism. Every subsequent research in this direction, however, has yielded negative results (see Manai (75)). The parasitic theory has been discussed again more recently by Lusena (62, 63) and by Tocco (100) but from

ment, and a lower layer which is granular. In this sediment are frequently observed hyaline, granular and sometimes epithelial casts, whose granules show a positive chemical reaction for iron. In the urine of some patients red blood cells have also been observed by Macciotta (64), McCrae and Ullery (77), and Hutton (49).

*The stools* Diarrhea is often present, but more frequently in the ingestion cases. The stools show usually an increase in the percentage of stercobilin (Manai (75)) and may show evidence of blood, as in the case reported by Hutton (49).

#### CLINICAL VARIETIES OF ATTACKS

Manai (75) describes *ambulatory, mild, severe, and very severe* forms. The very severe forms may be subdivided, depending upon the predominant condition, into *comatose, hemorrhagic, lightning-like, and anuric*.

Manai (75) also recognizes other forms which are of interest. The first of these is accompanied by *urticaria*, with severe itching, chiefly of the face and hands. Another type is purely *icteric*, without any apparent hemoglobinuria, since the hemolysis is much less severe.

In milder cases the jaundice may even be absent, and the attack is revealed only by *headache, dizziness, diarrhea*, and by an increase in the excretion of urobilin and stercobilin. Still milder forms are frequently observed in patients who have suffered repeatedly from typical attacks. In some patients *headache, dizziness, malaise, nausea, and low blood pressure* may last a few hours only, thus exhibiting a chiefly *vascular picture* (59). In others the chief symptom is headache, often assuming the characteristics of *migraine*. A slight rise in temperature, leucopenia with eosinophilia, and a diminution of the platelets were observed by Manai (75) in many patients with milder forms.

During the months in which the plant blossoms these milder forms are very frequent, disappearing somewhat later in the year.

#### MORTALITY

Death occurs almost only in children. In these, however, the rate is fairly high, reaching about 8 percent according to Fermi (35).

proteins could act as allergens. The allergic theory was later advocated after experimental researches by Lotti and co-workers (54, 55, 56, 57), from an anatomical standpoint by Guccione (48), from a clinical viewpoint by Biddau (13, 14, 15, 16), Gasperini (42) Chieffi (20, 21) Preti (95, 96, 97) Manai (70, 71, 72, 73, 74, 75), Macciotta (64, 65, 66), Auricchio (3, 4) MacCrae and Ullery (77), and Hutton (49). The latest investigations suggesting the correctness of this theory were accomplished by myself and my co-workers Pazzi and Rubino (58, 59, 60, 86, 87, 88, 89).

### *1. Experimental evidence for the allergic theory*

Lotti and Manai (56) sensitized rabbits by intravenous injections of extracts of flowers and seeds of fava beans. A subsequent reacting intravenous injection was followed by attacks similar to those of man.

Hemoglobinuria was more easily provoked by extracts of the dried seeds and convulsions by extracts of the flowers. Sensitization with one of the extracts was followed by shock only with a reacting injection of the same extract. Later Manai (75) succeeded in provoking attacks of hemoglobinuria by feeding rabbits with fava beans and administering again, after an incubation period, the same substance, either by mouth or by injection. In a later series of researches, Manai succeeded in provoking an allergic shock by first injecting serum of sensitized rabbits, and later extract of fava beans. He explained this phenomenon by assuming a passive transfer of sensitization from rabbit to rabbit. Much more recently Piana (91) sensitized animals with extracts of fava bean pods. Three cubic centimeters were injected subcutaneously in rabbits at a single dose. A second injection performed 16 to 18 days later caused attacks of hemoglobinuria and death. Without a previous sensitizing injection, a dose of extract five times larger failed to cause any trouble.

It is my belief that some objections should be advanced to these experiments. One obstacle to experimental study is that the principles of fava beans eliminated in the urine of rabbits often give positive reactions to guaiac and benzedine (Lotti and Manai (56)). Consequently it is necessary to evaluate hematuria by means of spectroscopic analysis, a technique which was not always followed by the authors. Extracts of fava beans possess a severe toxic action on rabbits, often causing death of the animals at the first injection. Ex-



a somewhat different standpoint. As a matter of fact the former suggested allergy to parasitic proteins, the latter toxic action of parasitic substances.

#### TOXIC THEORY

This represents the oldest theory, but has been advocated even recently by some authors. Their concept is that favism is a kind of *alimentary poisoning*. Some unknown poison, contained in the seeds and flowers, is capable of provoking the attacks in sensitive people, even in a very small quantity. Among the recent authors, Ferrannini (31, 32, 33), Atzeni-Tedesco (2), Mameli-Calvino (69), and Tocco (100), are the chief advocates of the toxic theory. Ferrannini believes that different kinds of fava beans may or may not contain the hypothetic toxic substance. Mameli-Calvino described a substance yielding some chemical reactions of cyanogenetic glucosides. Tocco very carefully studied all the parasites of the plant, fruit, and flower, comparing the effects of the extracts on frogs. Some facts, however, cannot be explained by the toxic theory, for example, in inhalation attacks the amount of inhaled active substance is so small that, if poisonous, its action should be fatal for everybody. Again, attacks may occur in nursing children without coexisting symptoms in the mother. Moreover, the alleged excessive toxicity of the Sardinian seeds is denied by the fact that people born on that island may experience attacks anywhere, after ingesting fava beans grown elsewhere. Skin tests on favism patients with extracts of fava beans grown in different countries showed no difference in the intensity of the reaction (Pazzi (86)).

#### ALLERGIC THEORY

This theory is actually the most commonly advocated, and most logical. Pesci (90) in 1921, observing some similarity between favism and other paroxysmal hemoglobinurias, in which allergic mechanisms seemed to be demonstrated, was the first to advance this theory. Lusena (62) confirmed this hypothesis by pointing out the short duration of the incubation period, the innocuousness of the substance for most individuals, and the extremely small doses which may be sufficient to provoke the attack. He thought, however, that parasitic

too recent During an attack caused by inhalation, however, positive skin reactions to fruit extracts might be present Old people showed positive reactions to these extracts more rarely than children and young people Extract of cooked seeds usually gave a negative reaction in patients showing a positive reaction to raw seeds

(c) Extracts of *flowers* often gave a positive reaction in patients suffering from inhalation attacks, but only if the previous attack was not too recent During an attack caused by ingestion positive reactions to extracts of flowers might be present

(d) Reactions to *leaves* were much rarer and weaker than to flowers, but were usually present in patients reacting to the latter

(e) A positive reaction to *parasites of dried seeds* was present in some patients, usually adults or old people exhibiting mild attacks The same was true for extracts of *dried seeds* containing parasites, but in a much greater percentage

(f) Extracts of fruits grown in various countries showed no appreciable differences

These studies suggest the existence of different allergens and the possibility of either a *simple*, or of a *multiple sensitization* Thus, during an attack the skin tests are usually negative for the allergen causing the attack (either flower or seed), but extracts of other plant parts are still positive During convalescence the test for the allergen causing the attack gradually becomes positive Quite probably the allergens are *two* one is present in the pods and seeds of fava beans, the other in the flowers and, in much smaller concentration, in the leaves It is my opinion that they represent two kinds of differentiation from a fundamental single type of protein Drying of the seeds causes an attenuation of the antigenic properties, long cooking a nearly complete denaturation of them

The allergen of the parasites seemed of no practical clinical importance, despite the fact that there may be some sensitization to their protein Moreover, the possibility that the reaction is due to bean proteins contained in the digestive tract of the parasites cannot be excluded

Only the proteins of *Vicia faba* seem able to provoke hemoglobinuria They are present in every part of the plant, attaining, however, greater activity and slightly different character, both in the flowers and seeds

tracts of the flowers often give lesions of the liver. A single injection of an extract of dried beans may cause hemoglobinuria. Hemoglobinuria is obtained much more easily by extracts of dried seeds than by those of fresh seeds. This is in striking contrast to the clinical observation that only fresh seeds cause really severe attacks of hemoglobinuria in man. Moreover, hemoglobinuria may be provoked in rabbits not only by extracts of fava beans but also by those of lima beans, which never cause attacks in man. Therefore, I believe that, in spite of the fact that some of the manifestations shown by the animals were probably allergic, others were probably of a toxic nature. A more extensive study of plant allergens on various animal species closer to man would clarify this point.

## 2 Clinical studies

Association between favism and some allergic conditions was described by Auricchio (4), who noted favism in patients whose relatives suffered from urticaria, bronchial asthma and hay fever. The case of T. V. Campagna had allergic troubles caused by grass pollen.<sup>7</sup> Eosinophilia has been observed in patients some days after the attack by Macciotta (64) and Manai (75), and, in post mortem examinations, by Guccione (48).

The first skin tests on patients by Manai (75), Chieffi (20), Biddau (13, 14), Gasperini (42), and Hutton (49), gave uncertain results. Intradermal tests gave a positive result in the case reported by McCrae and Ullery (77), but the injected dose was exceedingly high and no control is mentioned. More systematic researches were accomplished by my co-worker Pazzi (87). He studied forty-four patients by means of skin tests with various extracts of flowers, pods, fresh seeds, leaves, dried seeds, and of the parasites of the latter. His results were the following:

(a) A positive reaction to *all extracts* was never obtained in patients during an attack, but was attained a few weeks after the cessation of the attack. The patients showing reactions were susceptible to attacks either by inhalation or by ingestion.

(b) Extracts of *fresh fruits* often gave a positive reaction in patients suffering from ingestion attacks, but only if the previous attack was not

<sup>7</sup> Personal communication.

of the P substance in the urine of fava patients was thus demonstrated

Experiments dealing with the "passive transfer of sensitization" from man to rabbits seemed to Lotti and Manai (56-57) to yield a positive result. This kind of experiment, however, may be criticized on the basis of species difference. New researches were accomplished by my co-workers Pazzi and Rubino (89), who injected the serum of patients with favism either into the skin of normal persons (Prausnitz-Küstner method), or into the ears of normal rabbits (Lehner-Rajka method). A subsequent skin test with fava bean extracts in the injected areas was then performed. A local reaction was obtained if serum of patients already convalescent, or for some time previously without attacks, was employed. Either a negative or a doubtful result appeared if the serum employed had been taken during the attack of favism. The same was true when P substance extract was used instead of bean extract in this type of intradermal test. These researches were later confirmed by Marcialis (76), who succeeded in obtaining a "passive transfer" employing Waltzer's technique of feeding normal children with fava beans, then performing intradermal tests with serum of favism children.

In spite of the fact that many problems still require solution, the possibility of an allergic mechanism in the pathogenesis of favism cannot longer be denied. The existence of such a mechanism was still questioned in 1933 by Frugoni and Melli (118), who did not admit a "specificity of allergen," namely that only fava bean proteins could cause hemolytic attacks after sensitization and no other clinical pictures. An answer to this objection may be advanced by pointing out that (1) Other vegetable proteins may cause hemoglobinuria. Some cases were reported by Fermi (35), one was clearly described to me by a patient (59). (2) Fava beans may cause different clinical pictures.<sup>5</sup>

In favism a certain importance can be attributed to malaria. Nearly all people suffering from favism have had malaria and have had malarial ancestors. The relationship between favism and

<sup>5</sup> Some of them were described by Manai (75) (urticaria, diarrhea, headache), one by me (59) (malaise and cardio-vascular collapse), one by Parlato (132) (bronchial asthma). This last important observation was made in California.

A second type of research was accomplished by my co-worker Pazzi (86) in an attempt to isolate the so-called *P substance of Oriel* in the urine of patients during attacks of favism

This substance, a protease, was described by Barber and Oriel (107) as present in the urine of many patients with different allergic diseases, and was extensively studied by Oriel and his co-workers. In several successive contributions they reported the results of intradermal injections of this substance in normals and in persons with allergic conditions. Later they sensitized guinea pigs to the P substance of some patients, then tried on the isolated uterus the reaction to P substance from the same and other patients. A slight skin reaction to P substance was present in all subjects. However, only allergic individuals showed a definite and intense reaction, with a maximum in those exhibiting sensitization for the same group of proteins (group specificity), as evidenced by clinical signs and laboratory tests.

The P substance extracted by Pazzi from the urine of 7 cases of favism was tested in 19 patients with favism, with a positive result in nearly all for a dilution 1:10,000. Physiologic salt solution in patients with favism gave negative results. No skin reaction was obtained in patients suffering from other diseases. Therefore the necessary controls were present.

The positive reaction obtained in patients with favism was very evident and appeared within five to ten minutes and caused a wheal about 3 to 5 cm. in diameter. This "early reaction" may be followed by a "late reaction," consisting of progressive extension of the edema to a large area with very slight hyperemia involving sometimes about two-thirds of the forearm. This "late reaction" lasted from 12 to 36 hours and is something that appears to be characteristic of favism, since it has not been described by Oriel in his writings on asthma and urticaria. A further study was made of the reaction to P substance from favism of the skin of normal people who had previously been submitted to "passive transfer" by local injection according to the technique of Prausnitz-Kustner of the serum of patients who had had attacks of favism. A positive reaction was obtained in some of them. Control tests with the P substance of favistic patients on a patient with pollen asthma who was intradermally reactive to homologous P substance gave a negative result (Pazzi (86, 88)). The specificity

In 1914 Pesci (136) observed that during anaphylactic shock a diminution of the red blood cells occurred. This was caused by hemolysis which continued throughout the second day. Slight anemia and hemoglobinemia were also described by Civalleri (115) in 1916 in rabbits with experimental serum anaphylaxis. Later on Bechhold (111) showed that not only different osmotic actions, but any physical or chemical change of the colloidal complex of plasma may provoke hemolysis. Thus he demonstrated that any change affecting the swelling state of the three fundamental components of the red cells (proteic stroma, lecithin, cholesterol) will cause hemolysis.

Micheli (129) in 1910 had already advanced the theory that some kind of auto-anaphylaxis was responsible for the attacks of paroxysmal hemoglobinuria a frigore. A few years later Widal, Abram and Brissaud (147, 148) studied many cases of this disease. Without denying the chief facts ascertained by Donath and Landsteiner they tried to include these attacks in the large field of allergy. They showed that often muscular pain and cramps, joint pains, nausea, vomiting, itching, erythema, urticaria, and acute edema may be present during the attack. A careful study showed further that when the patient is exposed to cold a series of phenomena initiate the attack: low blood pressure, leukopenia, inversion of the differential white cell count, decreased coagulation time, faulty retraction of the coagulum. These changes constitute the so-called *hemoclastic crisis* and occur at first, as a "plasmatic stage" of the attack. In a second phase the red blood cells are attacked ("globular stage"), and the hemolysis occurs only in a third phase.

The hypothesis of the French authors did not exclude the importance, either of syphilis, or of cold, but gave a different explanation of their action. The former would be responsible for a more unstable plasmatic complex, the latter would modify some of the plasmatic components, and cause sensitization to them. Repeated exposure to cold would be followed by shock, with dissociation of the plasmatic complex, and subsequently by hemolysis and hemoglobinuria.

These researches were confirmed by many authors (Ricaldoni (137), Montagnani (131), Schiassi (140), and others), who not only found new evidence supporting the theory, but obtained some good results in desensitizing patients. They often found the typical signs of hemoclastic crisis and the subsequent stages of leukocytosis and eosinophilia. A similar theory was advanced in the explanation of quinine hemoglobinuria.

Following these experimental and clinical studies Pesci (136) advanced the hypothesis that the hemoglobinuria of favism shows only a marked increase of the phenomena occurring in every experimental

other hemoglobinurias is shown by the observation of Pucci (98) and of Auricchio (4), and by my observation (59), of families in which many people had suffered from favism and from quinine hemoglobinuria in different periods of their lives. In my observations skin tests demonstrated sensitization to fava bean seeds.

It is possible that a toxic element may be concerned in the syndrome of favism. The very small amount of protein necessary to produce an attack leads, however, to grave doubt as to this possibility in man, even if fava proteins show an important action when injected in rabbits.

Some points dealing with the allergens, the predisposing factors, the sensitization, the cause of the attacks, and desensitization have been discussed in detail in a previous paper on the subject (Luisada (59)).

*Sensitization* can occur in persons at any age. It is, however, much more common during infancy, due presumably to the fact that mother's milk and goat's milk may contain fava bean proteins (Luisada (59), Frongia (38), Macciotta (64)), and possibly because the protective power of the liver is less developed. A hereditary sensitization has also been suggested in favism and may be admitted as a distinct possibility. According to the views of Jordan (119) the liability to react hypersensitively is transmitted in animals from mother to offspring, the young of actively sensitized guinea pigs being themselves hypersensitive. The male does not transmit this quality. According to Coca (115) inherited hypersensitiveness may occur in human beings (atopy). Therefore this possibility which previously was presented as a purely theoretical problem, is now open for discussion.

*Desensitization* occurs usually for a short time during and after attacks. During this period patients can even ingest fava protein without new symptoms, as in Gasbarrini's experiment (40), and skin tests, as well as passive transfer experiments are often negative. During life, if the patient survives several attacks, complete freedom from new attacks may develop spontaneously. Even when this degree of immunity does not occur, most patients have less severe attacks as they grow older.

The conception of an "allergic hemolysis" requires some further discussion.

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shock Fava proteins, instead of acting primarily on plasma and tissues, would act directly on the red cells In the usual anaphylactic shock physical changes of the plasma would cause some hemolysis, in favism more direct changes of the red cells would occur, causing therefore an extensive destruction of the red cells themselves

Further studies are necessary for the complete explanation of hemoglobinurias Amongst them I believe that those on favism will contribute much to the clarification of the general problem of hemolysis

*Treatment* Treatment of the hemolytic attack is very important since this often endangers life and always causes severe anemia

Hypodermic injections of 10 cc of normal horse serum were tried by Fiha (37), Macciotta (64), Auricchio (4), Chieffi (21) with good results Association of horse serum and mother's blood was employed in children by Cocchi (24) and by Chieffi (21) The latter and Auricchio (4) used in other cases only mother's blood (10 cc by intramuscular injection), and in some patients this treatment was associated with intramuscular or intravenous injection of magnesium thyosulphate 10 percent The results seemed good Epinephrine intramuscularly and calcium gluconate intravenously were tried by McCrae and Ullery (77) and by Hutton (49) with good results Blood transfusion was tried also by them, and by Biddau (16) Spontaneous recovery of normal blood values following the termination of the hemolytic process should occur unless inhibited by a pre-existing nutritional anemia In any event iron may be given, but liver therapy is not indicated for any specific effect on blood formation

Between the attacks many attempts have been made to avoid their recurrence An old empiric method used in Sardinia is based on drinking an infusion of dried fava beans or rubbing the skin with it If an allergic mechanism is present, this method would represent an empiric attempt at desensitization, and the low activity of the dried seeds would make their use preferable More rational attempts at specific desensitization have been tried by Manai, but the results are not yet available Extensive research in this direction should be advised

In the absence of a specific treatment, abstention from contact with fava proteins, especially from April to August, is the most effective preventive measure

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# ADULT SCURVY AND THE METABOLISM OF VITAMIN C<sup>1</sup>

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land in 1535 suffered from scurvy but did not recognize it as such. It was recorded that in the month of December "an unknown sickness began to spread itself amongst us after the strangest sort that ever was eyther heard or seene in so much as some did lose all their strength, and could not stand on their feete, then did their legges swel, their sinnowes shrink as black as any cole. Others also had all their skins spotted with spots of blood of a purple colour, then did it ascend up to their ankels, thighes, shoulders, armes and necks, their mouths become stincking, their gums so rotten that all the flesh did fall off even to the roots of the teeth which did almost all fall out. With such infection did this sickness spread itselfe in our three ships that about the middle of February of a hundred and tenne persons that we were there were not tenne whole so that one could help the other, a most horrible and pitiful case." On this occasion a cure was discovered consisting of a decoction of sassafras bark and leaves. Vogel (168)

In the 16th century treatises appeared on scurvy by Claus Magnus, Ronsseus, Echter (the first physician to describe scurvy) and Wierus. The colonists in the northern part of America were also afflicted with scurvy. The French for instance were reported to have met with such a mortality during the severe winters in Canada that they frequently debated abandoning this settlement. This was true also of the English and their settlement in Newfoundland. Indeed it was scurvy that forced the early settlers in Hudson Bay to discontinue their efforts to colonize that region. George Whetstone, a soldier of fortune who in 1598 wrote one of the first works on tropical medicine, wrote of scurvy that "it is so ordinary at sea as it hath been seldome seene, any Ship or Pinnace to be foure months upon any voyage but some of the Companie have had this disease." It might not be amiss at this point to note that the duration of time necessary for scurvy to develop on almost all these voyages was about four months. In spite of the fact that Ronsseus in 1564 referred to the use of scurvy grass, watercress and oranges as a cure for scurvy, antiscorbutics were not used to any extent until the 18th century and scurvy continued to be accepted as one of the inevitable accompaniments of life at sea. As a matter of fact, as Vogel (168) points out, 'an extraordinary experiment in practical therapeutics as well as a demonstration of sagacious statecraft was in preparation when in February 1600 Elizabeth

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With the isolation and identification of vitamin C in 1933 the study of scurvy gained a new impetus. In the next six years several hundred papers appeared in the literature on various aspects of ascorbic acid metabolism. This article, which reviews the present knowledge of scurvy, also includes unpublished studies on adult patients with scurvy.

The origin of the word "scurvy" is obscure and appeared in the middle ages as a folk-word (24). The first definite description of scurvy is credited to Hippocrates. He described a large number of men in the army who suffered with pains in the legs and gangrene of the gums which was accompanied by loss of teeth. The next report of scurvy was by the crusaders. During the middle of the thirteenth century the soldiers under St. Louis suffered from an epidemic which they attributed to a species of eel they had consumed during Lent. De Joinville, who accompanied the crusaders, in describing this disease referred to the lividity and spongy condition of the gums often-times leading to gangrene necessitating cutting away the dead flesh in order to enable the people to masticate. He also writes of their debility, their tendency to faint, and the black spots on their legs (76).

With the Renaissance and the development and spread of education scurvy was reported both on land and sea. At sea, "until long voyages were undertaken so that crews had to remain for months out of contact with the shore, scurvy was not a menace to the mariner, but, following the discovery of America and the Indies, ships sailed to distant ports of the world and the disease had the opportunity to develop." No mention is made of scurvy occurring in the voyages of Columbus but soon afterwards accounts of scurvy filled the logs of ships on long voyages. In 1497, while discovering the passage to the Indies by the way of the Cape of Good Hope, Vasco de Gama lost 100 of his 160 men because of scurvy. Magellan's crew was riddled by "the Plague of the Sea and the Spoyle of Mariners." In Lord Anson's circumnavigation  $\frac{4}{5}$  of his crew died as a result of scurvy and in others old wounds reopened that had been healed for many years. This is confirmed by some of our recent knowledge regarding the role of vitamin C in wound healing (96). Jacques Cartier's crew on their voyage to Newfound-

fortunates had to swallow a bolus the size of a nutmeg of a terrific electuary compound of garlic, mustard seed, radish, balsam of Peru, and gum myrrh three times a day. In six days the lucky ones who had got the oranges were well enough so that one was able to return to his duty and his companion was able to nurse the other members of the group. The rest, except those who had received the cider, showed little or no improvement." (16S)

Sir Gilbert Blane emphasized the scourge of scurvy and it was largely through his efforts that the British Admiralty finally agreed to the use of antiscorbutics. Blane, in addition, recognized the destructive action of heat on the antiscorbutic principle. In 1795, due to his insistence, lemon juice was made a regulation issue in the British fleet and after ten days at sea each man received a fluid ounce daily (approximately 15 mg of vitamin C). No regulations, however, were instituted for the merchant marine until 1854 and 1869.

On land innumerable epidemics took place in the 18th and 19th centuries. Those which were not attributed to military life or campaigns generally occurred in prisons, insane asylums, poor houses or houses of refuge and correction. Between 1556 and 1877, 143 land epidemics are described in the literature. Scurvy occurred extensively in the Crimean War, in our own Civil War, amongst the besieged in Paris during the Franco-Prussian War, and in the past World War. In the Russo-Japanese War, after the siege of Port Arthur, it was found that about one-half of the garrison of 17 000 men had scurvy. Scurvy has occurred in every land but has been particularly prevalent in northern sections where vegetation is scanty. It has occurred in epidemic form whenever the crop has failed,—in India, Arabia, Dutch Guiana, Ireland, and in the United States. (76)

Brown (20) in *A Naturalist at the Poles* stresses that it was not climate but scurvy that gave polar regions their bad name. 'At Cape Flora Dr Koertlitz was able to prevent scurvy because the leader and staff followed his advice and lived chiefly on bear meat and guillemots, but nearly all the men on board the *Windward* suffered from scurvy. They lived on tinned meat, tinned vegetables and any amount of lime juice.' The only ones who escaped were those who took bear meat whenever they could get it. Lime juice had long been looked on as an antiscorbutic, but in Bruce's experience it was valueless with-



laid the foundations for the British Empire in India by sending four ships down the Thames as the first expedition of the newly chartered East India Company. There were the usual delays at sea and the usual outbreak of scurvy so that months later when the little fleet reached Table Bay, Captain Lancaster of the *Dragon* after bringing his own ship to anchor, had to get out his boats and send men aboard each of his consorts to do the like for them as their crews were too weakened by the disease to make the effort. Of 278 men on board these ships 105 died, the healthy condition of the *Dragon's* men being due to the fact that their farsighted commander had taken along a supply of lemon juice and given 3 spoonfuls to each sailor every morning. This is evidence of the protective value of approximately 75 mgm of vitamin C daily.

The crystallization of the theories of scurvy came toward the close of the 18th century when three great naval hygienists, James Lind, Sir Gilbert Blane and Thomas Trotter of England, backed by the practical experience of a famous explorer, James Cook, insisted with such emphasis on the necessary reforms that the disease was finally brought under control. Lind's "Treatise of the Scurvy" (100), which appeared in 1753, remained the most comprehensive volume on the subject until Hess' monograph in 1920 (76). Lind believed that scurvy was due to a combination of factors of which the predominating was lack of fresh vegetables, but he also considered that exposure to cold and dampness was of great importance. "As a result of many observations he convinced himself that oranges and lemons were the best antiscorbutics, the former slightly preferable, and he describes a practical experiment made on H M S *Salisbury* in 1747. He took twelve scurvy patients, in whom the disease was as similar as possible, kept them all together in the same part of the ship and on the same diet and tried on them the six different forms of treatment then in vogue. Two of them were given a quart of cider a day, two others took twenty-five drops of elixir of vitriol 3 times a day and also used a mouth wash acidulated with the same preparation. Two more received spoonfuls of vinegar 3 times a day, having their gruels and other foods well acidulated with it as well as their mouth wash. Two others were obliged to drink half a pint of sea water daily. Another pair were given two oranges and a lemon every day and the remaining two un-

Another characteristic property of active solutions was their power to reduce a number of reagents. Bezssonoff (15) found that the active agent reduced phosphomolybdotungstic acid. It reduced ammoniacal silver nitrate and decolorized potassium permanganate in the cold. In 1930 (163) the redox dye, 2-6 dichlorophenolindophenol was introduced for the determination of the reducing activity of substances with antiscorbutic activity. This made it possible to determine conveniently—at this time by titration—the reducing capacity of foods and various tissues. In the early work Zilva (184) thought that vitamin C itself did not reduce indophenol, but that the decolorization of the indicator was due to a reducing substance closely associated with the active principle which tended to prevent oxidation.

About this time the hope of isolating the vitamin was realized, but in a manner that had not been foreseen. Moreover, the antiscorbutic character of the substance thus isolated was not appreciated until some years later. Engaged in an investigation on the part played by the adrenal cortex in biological oxidation, Szent-Györgyi (159) isolated from the cortex a hexose derivative with strong reducing power—hexuronic acid. This compound he found also in vegetables and fruits where it appeared to function with peroxidase systems, thus associating the adrenal cortex with this oxidizing mechanism. Among other observations he recorded that hexuronic acid decolorized indophenol—a fact that prompted him to suggest that the acid was probably identical with the reducing substance described by Zilva. Tillmans (164) suggested that the reducing substances that reacted with 2-6 dichlorophenolindophenol and vitamin C were the same, and that the latter and the hexuronic acid of Szent-Györgyi were identical. Shortly after this, King and Waugh (90) announced that they had isolated and crystallized a substance from lemon juice that in their opinion was hexuronic acid and that this acid had anti-scorbutic activity. Simultaneously Szent-Györgyi (158) examined an authentic sample of crystalline hexuronic acid obtained from adrenal cortex and found it to be potent as an antiscorbutic. It was soon proven beyond doubt that these crystalline products were the antiscorbutic vitamin. The observation that synthetic ascorbic acid synthesized from material with no antiscorbutic value was active as an antiscorbutic supplied the final and incontrovertible proof. This was accomplished in 1933

out fresh food On the Balaena, lime juice, "according to the act", was served out daily, yet every one on the way home had symptoms of scurvy which disappeared only after a diet of fresh potatoes which were taken on board at Portland

More recently, the epidemic character of scurvy has disappeared In the United States during 1920 to 1930 adult scurvy was called "Bachelor Scurvy" because it was found among bachelors who cooked their own meals and had certain definite idiosyncracies as regards food With the economic depression of the past decade the incidence of scurvy increased, and this increase was not confined to any one group

#### THE ETIOLOGICAL THEORIES OF SCURVY AND THE DISCOVERY OF VITAMIN C

As has already been stated, it was known for a long time that scurvy was due to faulty nutrition, but just which nutritional factor was responsible had not been determined Many theories had been suggested but most of them had died a natural death Among these was the Potassium Theory advanced by Garrod (57), the Citric Acid Theory suggested by Netter (114) and the Acidosis Theory proposed by Sir Almroth Wright There was also a Toxic Theory and an Infectious Theory suggested by some other investigators The approach to the problem gained new impetus as a result of studies on another vitamin Gryijn (63) continuing Eijkman's work suggested that beri-beri was due to a dietary deficiency and Axel Holst (80) in an endeavor to find out whether polyneuritic diets were able to produce this disease in animals other than birds, observed that guinea pigs developed a pathological condition distinctly different from polyneuritis This condition Holst and Frolich (81) were able to identify with scurvy When it became apparent that scurvy was a vitamin- or accessory-food-factor deficiency disease, the interest of the biochemists as to the nature and structure of this vitamin was aroused In the early work the citrus fruits were used as sources of the vitamin as they had always been considered 'specifics' against scurvy Lemon juice was concentrated by various means but the lack of stability of the vitamin hampered its isolation and identification It was found that the active principle was rapidly destroyed in oxygen and that the extracts were more stable in acid than in alkaline solutions (183)

Another characteristic property of active solutions was their power to reduce a number of reagents. Bezssonoff (15) found that the active agent reduced phosphomolybdotungstic acid. It reduced ammoniacal silver nitrate and decolorized potassium permanganate in the cold. In 1930 (163) the redox dye, 2-6 dichlorophenolindophenol was introduced for the determination of the reducing activity of substances with antiscorbutic activity. This made it possible to determine conveniently—at this time by titration—the reducing capacity of foods and various tissues. In the early work Zilva (184) thought that vitamin C itself did not reduce indophenol, but that the decolorization of the indicator was due to a reducing substance closely associated with the active principle which tended to prevent oxidation.

About this time the hope of isolating the vitamin was realized, but in a manner that had not been foreseen. Moreover, the antiscorbutic character of the substance thus isolated was not appreciated until some years later. Engaged in an investigation on the part played by the adrenal cortex in biological oxidation, Szent-Gyorgyi (159) isolated from the cortex a hexose derivative with strong reducing power—hexuronic acid. This compound he found also in vegetables and fruits where it appeared to function with peroxidase systems, thus associating the adrenal cortex with this oxidizing mechanism. Among other observations he recorded that hexuronic acid decolorized indophenol—a fact that prompted him to suggest that the acid was probably identical with the reducing substance described by Zilva. Tillmans (164) suggested that the reducing substances that reacted with 2-6 dichlorophenolindophenol and vitamin C were the same, and that the latter and the hexuronic acid of Szent-Gyorgyi were identical. Shortly after this, King and Waugh (90) announced that they had isolated and crystallized a substance from lemon juice that in their opinion was hexuronic acid and that this acid had anti-scorbutic activity. Simultaneously Szent-Gyorgyi (158) examined an authentic sample of crystalline hexuronic acid obtained from adrenal cortex and found it to be potent as an antiscorbutic. It was soon proven beyond doubt that these crystalline products were the antiscorbutic vitamin. The observation that synthetic ascorbic acid, synthesized from material with no antiscorbutic value, was active as an antiscorbutic supplied the final and incontrovertible proof. This was accomplished in 1933.

out fresh food. On the *Balaena*, lime juice, "according to the act", was served out daily, yet every one on the way home had symptoms of scurvy which disappeared only after a diet of fresh potatoes which were taken on board at Portland.

More recently, the epidemic character of scurvy has disappeared. In the United States during 1920 to 1930 adult scurvy was called "Bachelor Scurvy" because it was found among bachelors who cooked their own meals and had certain definite idiosyncracies as regards food. With the economic depression of the past decade the incidence of scurvy increased, and this increase was not confined to any one group.

#### THE ETIOLOGICAL THEORIES OF SCURVY AND THE DISCOVERY OF VITAMIN C

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arguments in favor of ascorbic acid deficiency as the specific etiological factor in scurvy. However, one final proof was still to be provided, i.e., the experimental production of full blown scurvy in human beings on a vitamin C free diet. This had been accomplished in several of the other deficiency diseases. For example, Goldberger (60) was able to produce pellagra experimentally in humans; Sebrell and Butler (145) have been able to produce cheilosis on riboflavin deficient diets, and Jolliffe (85) et al. have produced definite symptoms and signs of vitamin B<sub>1</sub> deficiency in normal individuals on thiamin poor diets. Where ascorbic acid was concerned there was less definite evidence of adult human scurvy occurring on a diet deficient *solely* in vitamin C. Cases of scurvy have been reported in patients on ulcer diets (39), which are practically devoid of ascorbic acid, but these diets also are low in certain other nutritional elements (e.g., Vitamin B<sub>1</sub> and certain proteins). Very recently Crandon, Lund, and Dill (33) placed a normal adult individual on a diet adequate in all the nutritional elements but completely lacking in ascorbic acid. After *four months* on this diet no evidences of clinical scurvy had appeared, although the plasma vitamin C had been zero for about two months, and the concentration of ascorbic acid in the white-cell-platelet layer had also fallen to zero. Biopsy of an eight-day old experimental wound at the end of the four months period showed no inability to form intercellular substance, and wound healing occurred at a normal rate. On the 134th day of the deficient diet, however, the patient developed small perifollicular hyperkeratotic papules over the buttock and thighs and on the 161st day of the deficient diet, the subject developed petechiae, and showed no healing of an experimental wound at this time (33). When crystalline vitamin C was added to the diet, the petechiae disappeared, the wound healed, and the subject felt much stronger, admitting that he had not realized how fatigued and weak he had become during the long period on the diet. This is the *first evidence* of the production of human scurvy under purely experimental conditions. On an otherwise adequate diet the production of clinical scurvy apparently requires about six months. How long it would take to produce hemorrhages of major proportions is not known.

Many observers had felt that adult human scurvy was not due simply to a deficiency of vitamin C alone. Thus Hess (76) claimed



The nature of the substance from which vitamin C is synthesized in animals or plants has not as yet been determined, nor have the organs or tissues responsible for the synthesis of vitamin C been identified. The suggestion that mannose might act as a precursor of vitamin C (65) could not be confirmed (73). King and his associates (111, 102) have found that a great many substances increased the excretion of vitamin C in rats. Among these were terpene-like cyclic ketones which were particularly effective in stimulating the excretion of ascorbic acid. For example, feeding 100 mg of d-carvone per day led to average excretion values as high as 16.5 mg per day. Normally rats excrete about 0.2 to 0.4 mg of ascorbic acid daily. Aliphatic compounds that were found to be relatively active were diisobutyl ketone, dipropyl ketone, and dimethylacetylcarbinol. In view of the great variation in molecular structure of the compounds, it is pointed out that these substances probably did not serve as direct precursors of ascorbic acid, but rather served to stimulate the synthesis of ascorbic acid from intermediate metabolites. On further investigation it was found that compounds used as nerve depressants accelerated the excretion of ascorbic acid in rats. Among these were the barbituric acid derivatives and paraldehyde and chlorotone and some of the antipyrenes. Phenols, salicylates, sulfanilimide, and sulfapyridine were only slightly active. It is interesting to note that rats continued to synthesize considerable amounts of vitamin C for three months in response to the feeding of 20 mg daily of either sodium phenobarbital or chlorotone. King and his associates point out that no evidence was obtained which would indicate that the urinary ascorbic acid was conjugated with any of the toxic substances fed and they thought that its endogenous production might be related to the animal's detoxication processes. The possibility that ascorbic acid might act as a detoxifying agent had already been suggested in relation to poisons such as arsenic (28), benzene (23), lead (79) and phenol (93). Although it is possible that ascorbic acid may act as a detoxifying agent, the fact that King et al. found no conjugated forms of ascorbic acid with any of the toxic substances used in their feeding experiments, does not permit one at the present time to do more than mention this role as a possibility.

In the species of animals capable of synthesizing vitamin C, the balance of evidence (102) is in favor of an endogenous origin from



that some other factor existed apart from the mere antiscorbutic value of the diet, which at times exerted a potent influence on the development of scurvy. According to Hess, "cases developing in spite of a moderate amount of antiscorbutic food and others not responding to the addition of vegetables, fruits, or even crystalline ascorbic acid to the diet, although not numerous, have been reported by too many experienced observers to be disregarded." Lind (100) always felt that scurvy was due to a combination of factors of which faulty nutrition was the foremost but not the sole one. He stressed the necessity of exposure to cold and dampness. The recent work of Crandon et al. (33) proves conclusively that scurvy is due to the deficiency of vitamin C in the diet but undoubtedly the onset of the symptoms of scurvy on such a diet may be precipitated by certain factors, such as infections and hyperthyroidism. In the case of infections there is probably an increased demand for vitamin C imposed on the body by the infectious disease, or the toxins elaborated might act on the weakened vascular tree and produce the picture of scurvy. Trauma also seemed to play some part in the development of scurvy among the mariners. During the first World War scurvy often appeared among those suffering from dysentery and here the poor absorption of antiscorbutics may have been an important etiological factor. In support of this, Chinn and Farmer (26) have recently shown that in diarrhea large amounts of ascorbic acid may be lost in the stool.

That certain drugs may be instrumental in the production of scurvy has also been suggested. Thus Kimball and Horan (89) claim that 51 per cent of all epileptic cases treated with dilantin (sodium diphenyl hydantoinate) develop gum changes similar to those found in scurvy. They ascribed these changes as due to a deficiency of vitamin C since the blood serum ascorbic acid paralleled the severity of the gum hyperplasia. Much doubt, however, has been thrown on Kimball's contention by Gruhzit (64).

#### DISTRIBUTION AND ORIGIN OF VITAMIN C IN THE BODY

As pointed out by King (91) in his review on *The Physiology of Vitamin C*, of the extensive number of animals studied, only man, the other primates, and guinea pigs lack the capacity to synthesize ascorbic acid. At no period in the life cycle of human beings is there any evidence that the synthesis of vitamin C occurs (91).

The distribution of the vitamin in body tissues is similar in all the species thus far studied, including man (13). It has been found that tissues with high metabolic activity have a high vitamin C content (182). Thus in order of decreasing concentration of vitamin C is the pituitary body, corpus luteum, adrenal cortex, young thymus, liver, brain, testes, ovaries, spleen, thyroid, pancreas, salivary glands, lungs, kidney, intestinal wall, heart, muscle, spinal fluid, and blood (table 2). The concentration of vitamin C in animal tissue is apparently related to the rate of activity of the tissue and its age (182). Yavorsky et al (182) found that the older the tissue the lower was its ascorbic acid

TABLE 2  
*Vitamin C Content of Human Tissues in Different Age Groups\**

	Mg per gm				
AGE GROUP	1-30 days	1-12 months	1-10 years	11-45 years	46-77 years
NUMBER OF CASES	11	9	11	17	19
Adrenal	0 581	0 525	0 550	0 393	0 230
Brain	0 460	0 189	0 433		0 110
Pancreas	0 365	0 304	0 225	0 152	0 095
Liver	0 149	0 148	0 163	0 135	0 064
Spleen	0 153	0 112	0 157	0 127	0 081
Kidney	0 153	0 122	0 098	0 098	0 047
Lung	0 126	0 057	0 058	0 065	0 045
Heart	0 076	0 049	0 042	0 042	0 021
Thymus	0 304	0 319	0 190		0 046

\* Yavorsky, M, Almaden, P, and King, C G, The Vitamin C Content of Human Tissues J Biol Chem, 106, 525, 1934

content. Plaut and Bulow (122) reported that the vitamin C content of cerebrospinal fluid in humans paralleled the dietary intake of the vitamin. This parallelism had already been established for the plasma ascorbic acid and dietary intake. The vitamin C content of the salivary juice bears no definite relationship either to dietary intake or to plasma concentration (3). The vitamin C content of sweat (29), aqueous humor (135), gastric juice (119), and nasal secretions (115) in humans has been determined.

Vitamin C is present in relatively high concentrations in nerve tissue, the highest being found in the medulla of the adrenal, the brain, and

tissue metabolites similar to that observed for glucuronic acid by Lipshitz and Bueding (101). In studies in which dogs and rats were employed, we have observed that when each species of animals consumed daily diets which were similar in quantity and character the

TABLE 1

*Average 24-Hour Excretion of Vitamin C and the Fasting Plasma Levels of Vitamin C in Normal Dogs on Similar Diets (Vitamin C-Free)*

DOG NUMBER	WEIGHT	NUMBER OF DAILY OBSERVATIONS	AVERAGE DAILY URINARY EXCRETION, VITAMIN C	URINARY EXCRETION PER KG BODY WEIGHT	FASTING PLASMA LEVELS, VITAMIN C	
					Number of observations	Average
	kg		mg	mg		mg per cent
220	10.25	14	64 ± 9.0	6.3	5	0.22 ± 0.06
227	9.25	7	67 ± 4.9	7.3	2	0.38 ± 0.06
207	15.75	13	304 ± 32	19.3	5	0.55 ± 0.09
211	12.25	17	189 ± 21	15.4	8	0.65 ± 0.07
197	11.25	10	232 ± 17	20.6	7	0.62 ± 0.14
193	9.0	21	163 ± 18	18.1	13	0.63 ± 0.08
215	11.75	1	300	25.5	1	0.89
218	13.0	6	319	24.5	2	0.94 ± 0.10

*Average 24-Hour Excretion of Vitamin C in Normal Rats on Similar Diets (Vitamin C-Free)*

RAT NUMBER	WEIGHT	NUMBER OF OBSERVATIONS	AVERAGE DAILY URINARY EXCRETION, VITAMIN C	URINARY EXCRETION PER KG BODY WEIGHT
	gm		mg	mg
1	288	14	1.3 ± 0.1	4.5
2	270	14	3.4 ± 1.2	12.6
3	290	14	5.3 ± 1.3	18.3
4	270	14	2.5 ± 0.4	9.3
5	273	14	3.2 ± 0.6	11.7
6	202	6	1.3 ± 0.3	6.4
7	221	6	2.6 ± 0.6	11.8
8	234	8	2.8 ± 0.7	12.0

plasma levels (in dogs) and urinary excretion of vitamin C varied over a rather wide range. The findings presented in Table 1 suggest that in dogs and rats the synthesis of ascorbic acid is independent of any specific food and is probably endogenous in origin. As mentioned previously, neither the site of synthesis nor its mechanism has as yet been determined.

TABLE 3

*Ascorbic Acid Content of Foods*

These values have been obtained from the following sources: M. A. B. Fikar and M. H. Rescoe, *Tables of the Vitamin Content of Human and Animal Foods*, Nutrition Abstracts and Reviews, 1940, 9, 795; E. P. Daniel and H. E. Mansell, *Vitamin Content of Foods*, U. S. Dept. of Agriculture, Miscellaneous Publication No. 275; O. A. Besser, *Vitamin C—Methods of Assay and Dietary Sources*, J. of Am. Med. Assoc., 1938, 111, 1290

Food*	Ascorbic Acid		Food*	Ascorbic Acid	
	Range	Average		Range	Average
	mg./100 gm.	mg./100 gm.		mg./100 gm.	mg./100 gm.
<i>Breads</i>			<i>Fruits—Cordoned</i>		
Black	0-1	0	Melons		
White	0-2	0	Cantaloup	20-40	30
<i>Fruits</i>			Honey-bell	31	31
Apples		4	Honey-crisp	7	7
Green	2-3		Musk	7-18	13
Baldwin	6		Water	1-15	5
Duchess	6		Oranges		
Spy	10-11		Pulp	16-71	50
Gravenstein	3		Juice	22-59	50
Apricots, fresh	1-16	3	Peel	59-210	100
Avocado	7-44	13	Syrup	0	0
Bananas	1-15	2	Papaya	32-150	40
Blackberries	2-15	3	Peaches	1-26	7
Blueberries	6	6	Pears		
Cherries	3-17	8	Pulp	<1-10	3
Cranberries	10-18	12	Juice, canned	Trace	Trace
Currents			Pineapples		
Black	90-253	100	Fresh	10-20	20
Red	14-30	15	Canned	10	10
Dates, cured	0	0	Plums	<1-11	2
Figs			Pomegranates	6-16	11
Fresh	2	2	Raisins	0	0
Dried	0	0	Raspberries	15-30	15
Gooseberries	20-30	25	Strawberries	46-73	30
Grapes			Tangerines	10-46	30
Black	3	3	Nuts, all kinds	0	0
Green	1-3	2	<i>Vegetables</i>		
Juice	0	0	Artichokes	3-20	11
Grapefruit juice	26-65	40	Asparagus	10-72	25
Lemons			Beans		
Pulp	14-66	45	Green, snap	2-40	10
Juice	26-71	60	Lima	23-61	40
Peel	100	100	Yellow	7-26	15
Limas			Dried	0	0
Pulp	20-60	30	Beets	3-10	5
Juice	17-63	30	Broccoli	50-122	70
Mangoes	13-105	25	Cabbage	20-153	40

\* Unless otherwise indicated, these values are on fresh foods.

the pars intermedia of the hypophysis. Peripheral nerves are relatively poor in ascorbic acid (106).

The distribution of ascorbic acid in the elements of the blood has also been investigated (21). The white cell platelet layer is richest in ascorbic acid. The distribution ratio of the plasma concentration to red cell concentration varies with the state of vitamin C nutrition (21). Practically all the ascorbic acid in the plasma or the serum is in the reduced state (17), and the passage of ascorbic acid from the plasma into the red cells has been shown to be a slow process (74). This is not the case with the transfer of plasma ascorbic acid into the white cells. We have observed that within 20 minutes after the intravenous injection of ascorbic acid an appreciable rise in the concentration of ascorbic acid in the white cell layer occurred.

There is a high vitamin C content in tumor tissue during the period of rapid growth and with necrosis this decreases (88, 112, 167).

#### THE DISTRIBUTION OF ASCORBIC ACID IN COMMON FOODS

In general, the citrus fruits are the richest in vitamin C. Reference to Table 3 which has been compiled from determinations made by a large number of investigators shows the actual vitamin C content of various foods. The vitamin C content may vary greatly in different varieties of the same food, and it will also be affected by the treatment of the food. Open kettle cooking, wilting, and canning will reduce the content of vitamin C. Acidity of the food or its juices will protect against destruction of the vitamin.

#### PHYSIOLOGY

Harris and Ray (68) and more recently others (125, 180, 84, 70) have shown that in man as the dietary intake of vitamin C is diminished there is a corresponding decrease in the urinary excretion of the vitamin. When the body has become depleted of its normal vitamin C stores, administration of the vitamin first results in a storage of the vitamin in the various body tissues and when the deficiency in the tissues has been satisfied, urinary excretion again follows. Balance experiments of this kind provide a reasonably satisfactory means of clinically evaluating the various stages of vitamin C malnutrition. The net loss or difference between intake and excretion of the vitamin,

both in the human being and in the dog, the kidney excretes the vitamin by glomerular filtration and active tubular reabsorption. The reabsorptive mechanism for vitamin C appears to be limited by a maximal rate so that when the vitamin is presented to the tubules at a rate exceeding this maximum the excess is excreted in the urine. In a series of normal human beings studied by Smith et al (154), and Ralli and her associates (126),  $T_m$  values ranging from 1.20 to 2.10 mg of vitamin C per 100 cc of glomerular filtrate were observed. The average value observed in dogs, 0.52 mg of vitamin C per 100 cc glomerular filtrate, is of a much lower magnitude. When the vitamin is presented to the tubules at a rate below this maximum the excretion of the vitamin falls rapidly. At low plasma concentrations 97 to 99.5 per cent of the vitamin is reabsorbed. However, even at the lowest plasma level this reabsorption is never complete and there exists a minimal value for the clearance which is independent of the plasma concentration.

Faulkner (52) has observed a 'renal threshold' for ascorbic acid at a plasma concentration of 1.4 mg per cent. We have found that a rapid rise in the excretion of vitamin C occurs in the average individual when the plasma concentration exceeds 1.5 mg per cent (126).

Farmer and his associates (26, 27) have studied the fecal excretion of vitamin C. In the normal individual not over 6 to 10 mg of ascorbic acid are excreted daily in the feces even when large amounts are fed. However in patients suffering from gastro-intestinal disorders such as colitis and diarrhea or in infants following catharsis, much larger amounts of vitamin C were excreted in the feces when vitamin C was fed. This apparently was due to failure of absorption of the vitamin from the gastro-intestinal tract.

The most clearly established functional role of vitamin C in animal tissues is its relation to the physical state of the 'intercellular material' as described by Wolbach and his associates (174). This is discussed in more detail in the section on pathology. Vitamin C seems to be related to calcium metabolism in the laying down of osteoid tissue. Both roles are clearly of major importance in relation to growth and repair of bones and teeth, and it is evident that other tissues such as cartilage and white fibrous tissue are affected in a similar manner. Although the chemical mechanism through which the vitamin brings

TABLE 3—*Concluded*

TABLE 3—Continued

FOOD*	ASCORBIC ACID		FOOD*	ASCORBIC ACID	
	Range	Average		Range	Average
	mg / 100 gm.	mg / 100 gm.		mg / 100 gm.	mg / 100 gm.
<i>Vegetables—Continued</i>			<i>Vegetables—Concluded</i>		
Carrots	1- 41	3	Turnips	12- 54	30
Cauliflower	19-101	30	<i>Animal Products</i>		
Celery, stalks	1- 56	5	<i>Milk</i>		
Corn	4- 14	10	Cows' raw	0 2-4 3	2
Cucumbers	1- 18	2	Pasteurized	0- 1	0-1
Dandelions	8- 55	40	Skimmed	2	2
Egg plant	<1- 27	5	Butter	0- 1	0
Kale	34-164	50	Buttermilk	1	1
Kohl-rabi	16-108	70	Cheese	0- 5	0
Leeks	4- 33	15	Cream	0- 1	0
Lettuce	<1- 22	5	Milk, goats'	1- 9	2
Okra	10- 17	15	Milk, human	0 8- 11	6
Onions	3- 15	10	Colestrum, human.	7	7
Peas, fresh green	5- 60	15	<i>Fish</i>		
Peppers			Fresh cooked	Trace	Trace
Green, npe	12-330	180	Raw clams	8	8
Red, npe	69-280	230	Cod liver oil	0	0
Potatoes			Raw oysters	3- 8	3
New	15- 35	15	<i>Meat</i>		
Old	5- 23	7	Beef muscle, cooked.	Trace	Trace
Sweet	4- 91	8	Beef liver, cooked	10	10
Pumpkin	1- 22	5	<i>Miscellaneous</i>		
Radishes	10- 28	16	Beer	0- 2	0
Rhubarb	6- 37	18	Cider	1	1
Squash	3- 5	5	Sauerkraut	11- 19	16
Spinach	6-228	50	Juice	0- 5	3
Sprouts, Brussels	32-146	50	Yeast	0- 2	0
Tomatoes			Eggs	0	0
Whole	3- 5	25			
Juice	9- 40	30			

for a person in a state of "saturation", may be taken as an approximation or measure of the quantity of the vitamin normally utilized by the individual Ralli et al (125) studying the requirement of a series of normal individuals in this manner found that the normal subject is capable of utilizing about 100 mg of vitamin C daily

The mechanism by which the kidney handles the vitamin has been investigated by Ralli and her associates (126) They have shown that

did not observe any appreciable differences between the normal and the scorbutic animal. Recently Ecker and his coworkers (43) demonstrated a definite correlation between the complement titer of both guinea pig and human serum and the vitamin C content of such sera. In guinea pigs placed on a scorbutic diet, the complement titer dropped, paralleling the decrease in the ascorbic acid level of the serum. Following the feeding of ascorbic acid, the serum complement titer rose proportionately. This work needs confirmation in view of the fact that in the case of experimentally induced human scurvy studied by Crandon et al (33), no change in blood complement was observed, although there was no vitamin C in the white cells or plasma and the clinical signs of scurvy were well developed.

Perla and Marmorston (118) in a review of the role of vitamin C in resistance came to the conclusion that vitamin C had no relation either to natural antibodies or to the formation of immune antibodies. They think that in general subclinical scurvy may be associated with increased sensitivity of the skin to poisons, to tuberculin, and with an increased susceptibility of the body to anaphylaxis, but that frank scurvy may, on the other hand, be accompanied by suppression of the skin reaction and depression of the general susceptibility to anaphylaxis. In the absence of an established specific role of vitamin C in resistance to infection, the explanation of the decreased resistance to infection in scurvy may rest on the fact that there is some relationship between the presence of normal intercellular material and the maintenance of the natural resistance of the organism.

Seelock (146) has recently proposed that vitamin C is concerned with the normal metabolism of tyrosine, since he has been able to produce experimental alcaptonuria in guinea pigs on low vitamin C intake with the administration of tyrosine or phenylalanine. The administration of ascorbic acid decreased the alcaptonuria. This did not however, occur in a human alcaptonuric subject where the administration of large amounts of vitamin C failed to affect the alcaptonuria (147).

#### *Carbohydrate metabolism and vitamin C*

The relation of vitamin C to carbohydrate tolerance has been studied by several investigators. Most of this work has appeared in the



about this control of metabolism is unknown, Dalldorf (36) believes that the effect is on the gelling of the matrix

The presence of vitamin C in both the cells of higher plants and lower forms of life has been reported (18, 58, 59). The identification is based on the fact that vitamin C is the only naturally occurring substance that is capable of reducing acetic acid-silver nitrate solution in the dark at room temperature. These granules of reduced silver have been seen in the cells of unicellular animals and plants and in the cells of the higher mammals. The vitamin tends to show a higher concentration in young growing animal tissues than in older tissues (13). Bourne and Allen (18) also found that vitamin C tends to concentrate in the young growing tips of some fungal hyphae and that only a few granules remain in the older portions.

King (91) pointed out that although ascorbic acid *in vitro* has occasionally been shown to have a definite inhibiting or activating effect on such enzymes as cathepsin, papain, amylase, arginase, catalase, urease, tyrosinase and nuclease, there has not been consistent agreement in the observations reported and there is as yet no proof that the vitamin has any effect on enzymes *in vivo*. Most of the effects observed are probably due to the nonspecific acidity and reducing capacity of ascorbic acid. On the other hand it may be that some of the effects described do occur in animal tissue *in vivo*. This requires further investigation.

The theory that vitamin C serves primarily as a hydrogen-transport agent or respiratory catalyst, has not as yet been supported as regards animal tissue (157).

#### *The relation of vitamin C to immunology*

The question of the relation of vitamin C to resistance was originally suggested by the fact that scorbutic guinea pigs were observed to be prone to infection, and by the additional fact that infection seemed to precipitate the appearance of the signs of scurvy. The investigations of Koch and Smith (92), Hamburger and Goldschmidt (67), and Werkman, Nelson, and Fulmer (170) showed that there was no depression of natural antibodies (bacteriolysin, amboceptor, and opsonins) in scorbutic guinea pigs. Koch and Smith (92) found that there was a rise in complement in scurvy, but Hamburger and Goldschmidt (67)

depancreatized dogs was followed by a fall in the plasma level of vitamin C. A similar drop occurred in human diabetics but the percentage fall was less than in the dogs (unpublished experiments).

Some of the contradictory results reported on the relation of ascorbic acid and carbohydrate metabolism are due to the methods of measuring carbohydrate tolerance. At the present time there is no evidence that carbohydrate metabolism is significantly affected by vitamin C therapy or that it is impaired in scurvy, with the exception of Sigal and King's (151) observations of diminished glucose tolerance curves obtained in the course of scurvy in guinea pigs.

#### METHODS

The first methods used for determining the presence of ascorbic acid in foods were the biological ones. These depended on the degree of protection afforded by various vitamin C containing substances against the occurrence of the signs of scurvy in guinea pigs kept on a diet deficient in the vitamin. The three methods usually employed were the prevention method of Sherman and his associates (149), the curative method of Harris (69) and the tooth method of Hojer (78). While all these methods were specific they were only qualitatively accurate and required fairly long periods of time. Chemical methods for the determination of vitamin C were being studied by several investigators. In 1928 Tillmans (163) used the reduction of 2,6-dichlorophenolindophenol as a measure of the reducing capacity of extracts of foods rich in vitamin C and later for the determination of vitamin C itself. This method was confirmed and refined by other workers (69c) to provide a satisfactory means for measuring the concentration of ascorbic acid in various solutions. As a result of further study it was found that ascorbic acid was the only substance to react *immediately* with 2,6-dichlorophenolindophenol in acid solution. Other biologically occurring substances such as thiosulphate and cysteine, capable of reducing this indophenol do so at a much slower rate. The reaction between dichlorophenol and ascorbic acid can be accounted for solely on the basis of the difference in oxidation reduction potentials of their respective systems. While ascorbic acid is oxidized to dehydroascorbic acid, 2,6-dichlorophenolindophenol passes from its oxidized form (red in acid solution) to its reduced form (colorless).

foreign literature Sigal and King (151) noted a diminished tolerance in scorbutic guinea pigs, as measured by glucose tolerance curves. This impairment was improved following the administration of vitamin C. The observations of other investigators on this question of carbohydrate tolerance are somewhat contradictory. Boehncke (16) and Azerad (9) in humans, Yamada (179) in rabbits, and Addam (6) in rats and rabbits, found no change in the blood sugar level following the administration of vitamin C. Frada (55) reported that small doses of ascorbic acid caused a slight drop in the blood sugar in rabbits, but that larger doses were followed by a rise. DeLucia and Morelli (40) and Dessy (41) report a slight rise in the blood sugar level in rabbits following the administration of vitamin C. Wille (173) reported that ascorbic acid tended to elevate the blood sugar when it was at hypoglycemic levels. Pfleger and Scholl (120) considered that the action of insulin in both normal and diabetic subjects was intensified by the administration of ascorbic acid and that diabetic patients could be regulated with smaller doses of insulin when receiving ascorbic acid. On the basis of the data published it did not seem to us that the decrease in glycosuria was greater than that ordinarily observed in the course of treatment in the diabetic. Schroeder (139) reported that vitamin C and insulin caused a greater fall in the blood sugar level than did insulin alone. Actually the differences shown are very small. It is well to remember that the daily insulin requirement in diabetic patients may be affected by a variety of factors, and unless there is a change of considerable magnitude following the use of a therapeutic measure, no importance can be attached to it. In this respect it is interesting that Crandon (33) found the glucose tolerance curves and the sensitivity to insulin within normal limits in induced experimental scurvy in a human. Sebesta et al (144) and Turchetti (165) were also unable to observe any effect on carbohydrate tolerance following the use of ascorbic acid. Crandon (33) did observe however, that the removal of lactic acid from the blood was impaired during the scorbutic state, which is interesting in view of Duffau's report in 1937 (42) that the leg muscles of scorbutic guinea pigs contained more lactic acid than those of normal guinea pigs and that following vitamin C therapy the level in the scorbutic pigs returned to normal.

We noted (127) that the administration of insulin in normal and

depancreanized dogs was followed by a fall in the plasma level of vitamin C. A similar drop occurred in human diabetics but the percentage fall was less than in the dogs (unpublished experiments).

Some of the contradictory results reported on the relation of ascorbic acid and carbohydrate metabolism are due to the methods of measuring carbohydrate tolerance. At the present time there is no evidence that carbohydrate metabolism is significantly affected by vitamin C therapy or that it is impaired in scurvy, with the exception of Sigal and King's (151) observations of diminished glucose tolerance curves obtained in the course of scurvy in guinea pigs.

#### METHODS

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The reaction is best carried out at pH 4 because a) the redox potential difference between ascorbic acid and dichlorophenolindophenol is maximal at pH 4 and below, which assures completeness of the reaction, and b) indophenol is unstable below pH 3, while dehydroascorbic acid becomes increasingly unstable above pH 5.

Recently Butler and Cushman (21) have modified the method of Martini and Bonsignore (105) in which methylene blue is used for the determination of vitamin C in blood filtrates. Apparently a greater degree of accuracy can be attained by this method in blood filtrates than by the dichlorophenolindophenol methods.

To determine the ascorbic acid content of tissues, the tissues are extracted by grinding in an acid precipitant, which consists of metaphosphoric acid alone or in combination with other deproteinizing reagents. Ascorbic acid in the extract may then be determined by titration with indophenol or preferably in the photoelectric colorimeter (14).

The determination of whole blood ascorbic acid presents certain difficulties. Many investigators (44, 22, 87) have demonstrated that hemolysis decreases the concentration of ascorbic acid in plasma and that precipitation of whole blood by hemolyzing reagents such as trichloroacetic or metaphosphoric acid oxidizes ascorbic acid and invalidates the results. Lemberg, Legge and Lockwood (97) have shown that in hemolysis the liberated oxyhemoglobin enters into a coupled oxidation with ascorbic acid to form choleglobin. They also demonstrated that carbon monoxide will prevent this reaction. The older methods of Stephens and Hawley (156) and Emmerie and Van Eekeln (44) did not take these facts into consideration. Recently Butler and Cushman (21) have introduced a method which appears to offer promising results. It depends on the saturation of whole blood with carbon monoxide before precipitation with metaphosphoric acid. The ascorbic acid concentration of the filtrate is determined in a photoelectric colorimeter using methylene blue as an indicator. As previously mentioned, the methylene blue is about four times as sensitive an indicator as indophenol.

The determination of the vitamin C content of the white-cell-platelet layer consists in the separation and removal of that layer from the blood, weighing, and extracting with metaphosphoric acid. The

vitamin C content of the filtrate obtained after centrifugation is determined in the photoelectric colorimeter with indophenol as an indicator (21)

There are four methods in use for the determination of plasma ascorbic acid the macro and micro methods of Farmer and Abt (50, 49) which are simple titrations with indophenol of plasma filtrates after precipitation with metaphosphoric acid and the macro and micro methods of Mindlin and Butler (109) which make use of the photoelectric colorimeter and also take into account the final pH of the solution to be determined Kruse et al (94) have demonstrated that the methods involving the use of the photoelectric colorimeter have a far greater accuracy than the titration methods, and that the most accurate of all is the macro method of Mindlin and Butler We have modified the Mindlin and Butler technique so as to take into account the turbidity of the solution to be determined as recommended by Bessey (14) and have found that with this modification the method is accurate to  $\pm 0.02$  mg per cent

The use of potassium cyanide as an oxidation inhibitor (121) in whole blood is to be discouraged (56, 51, 34) It has been pointed out by several observers that its use is totally unnecessary, and indeed it may be a source of error

The most accurate method for the determination of urinary ascorbic acid is that described by Evelyn et al (48) as it differentiates between non-vitamin C reducing substances and vitamin C It also requires the use of the photoelectric colorimeter Time readings should be taken and an extrapolation to zero done Bessey (14) has simplified this latter procedure

The oxidation of urinary ascorbic acid depends on several factors oxygen tension, temperature, exposure to light, the acidity of the medium, and the presence of oxidative catalysts such as copper The addition of 8-hydroxyquinoline and 5 N-sulphuric acid to the urine and storage in the cold is the most effective procedure for preventing the oxidation of ascorbic acid in urine By this method the loss of titratable ascorbic acid is normally limited to 2 to 5 per cent over a period of 24 to 48 hours (12, 148)

Protein (148) and glucose (126) in the urine have no effect on the determination of urinary ascorbic acid

## PATHOLOGY

The pathology of scurvy in the human has been shown to be identical with that found in the experimental animal. The work of Wolbach and Howe (174) and others on experimental scurvy in the guinea pig has clarified the pathological changes occurring in this deficiency disease. As Wolbach has pointed out, the primary morphological effects of vitamin C deficiency occur in the intercellular substance of certain mesenchymal derivatives. According to Dalldorf, "these can best be described in terms of a prototype of these structures, loose connective tissue. Under normal conditions, the type cell, the fibroblast, lies in an amorphous ground substance within which fibrils (reticulum) are formed which may in turn become gathered into wavy bands of collagen. In this transformation the fibrils seem to become cemented together by a translucent matrix, the formation suggesting a colloid phenomenon, the setting of a gel." Dalldorf (36) believes it is this phase of the formation of intercellular materials which may be completely controlled by vitamin C. Thus in the scorbutic guinea pig, the ground substance and fibroblasts are present as in the healthy animal, but fibrin or collagen is not formed (Fig. I). When the deficiency is corrected, translucent bundles and masses of collagenous materials reappear within 18 hours. The formation of the intercellular material of bone (osteoid tissue) and of teeth (dentine) may be similarly controlled by withdrawing or supplying vitamin C.

The observations in the experimental animals are consistent with the observations of scurvy in humans (33, 82) (Fig. II). In scurvy, defective intercellular substances are seen in connective tissue, bone, and teeth, and are believed to occur in the blood vessels. The tendency is for the defective materials to form in the connective tissue in partial depletion, and for no intercellular material to form in complete deficiency. Just where the weakness occurs in the capillaries is not known. Whether the effect of the deficiency is on the sheath or on the endothelial cement substance has never been decided.

The anatomic manifestations of scurvy are greatly modified by two factors—growth and stress. For example, the bone changes so typical of scurvy in the infant do not usually appear in adult scurvy, whereas in the teeth of adults with scurvy the dentine is seen to be



FIG. 1. REPAIR BY AVASCULAR ORGANIZATION IN ABSOLUTE SCORBITIS

A strand of fibrin crosses the upper right-hand corner. Most of the cells in this field have probably emigrated from connective tissue surrounding the nerve shown in the lower border. Most of the fibroblasts are separated from one another. Five mitotic figures are on this field. Guinea pig operated upon on the 23rd day of vitamin C-free diet, killed on the 30th day of deficiency. Initial weight 315 gm., maximum weight 360 gm. and final weight 204 gm. Modified Gomori stain.  $\times 125$ .

Reprinted from S. Burt Weibach: Controlled Formation of Collagen and Reticulum. *Am. J. Path.*, 9, 689, 1933.



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rhages into the muscles, especially about the joints and into the joints are often present. In the eyes, ecchymoses of the eyelids and conjunctivae are common. The characteristic lesion in the skin is the peritollicular or petechial hemorrhage (Fig III). This is commonest wherever pressure exposes the weakness of the capillaries. Other lesions include bloodstained effusions into the serous cavities. There



FIG III ANTERIOR VIEW OF THE LOWER LEGS AFTER SIX MONTHS OF VITAMIN C-FREE DIET

Note the petechiae

Reprinted from J. H. Crandon, C. C. Lund and D. B. Dill. *Experimental Human Scurvy*. *New Eng J of Med* 223, 353, 1940

may be slight edema about the ankles. Enlargement of the heart may occur but the circulatory collapse that seemed to have been a feature of scurvy a hundred years ago was probably due to a deficiency of vitamin B<sub>1</sub>. Atrophy of the bone marrow has been reported in scurvy (104-113) although it is more often described as similar to the type seen in secondary anemia (107-166).

#### SYMPTOMATOLOGY

The symptoms of the disease begin as a rule insidiously with a feeling of general weakness and a loss of vigor. The individual tires

resorbed and porotic. This process commences about Tomes' canals. Such dentine as may be formed is inferior in appearance (osteodentin). The lesions of the gingiva occur only when teeth are present and are most severe about deformed or broken teeth. The gums become swollen and boggy and bleed easily. In severe cases of scurvy they have, at times, become so large as to hide the teeth and make mastication painful and difficult. Rarefaction of the alveolar bones



FIG II BIOPSY SPECIMEN REMOVED AFTER SIX MONTHS OF VITAMIN C-FREE DIET  
EOSIN AND METHYLENE BLUE STAIN ( $\times 350$ )

Note the newly formed fibroblasts having no intercellular substance between them. Old collagen may be seen at the bottom and extending down and to the right from the upper left-hand corner.

Reprinted from J. H. Crandon, C. C. Lund, and D. B. Dill. *Experimental Human Scurvy*. *New Eng J Med*, 223, 353, 1940.

results in loosening of the teeth. The gingival lesions commence on the papillae first as a hyperemia with dilated thin-walled vessels, with a tendency to intractable hemorrhages. Disintegration of the epithelium follows, along with infection and ulceration and granulation, and even gangrene. Lesions in the mouth are remarkably constant.

Fragmentation of the striated fibers of muscle and intense reparative efforts marked by multiplication of the sarcolemma occur. Hemor-

There may be either microscopical or gross hematuria. In the experimental production of scurvy in a young adult male, Crandon, Lund and Dill (33) noted the following sequence in the occurrence of the clinical signs of scurvy. The first to appear after 134 days of the vitamin C deficient diet were small perifollicular hyperkeratotic papules over the buttocks and posterior aspects of the thighs. This was followed almost immediately by fragmentation of the hairs, and it was noted that each papule contained an ingrown hair. About 25 days later, small perifollicular hemorrhages and petechiae appeared over the lower legs, which did not fade on pressure and many



FIG. V. SUBCUTANEOUS HEMATOMA ON THIGH IN A PATIENT WITH SCURVY.  
Reprinted from A. Nisenson and A. G. Cohen, *Adult Scurvy, Study of the Urinary Output of Cevitamic Acid*, *Am. J. Med. Sci.*, 194, 63, 1937.

of which occurred after standing. The gum changes were late in manifesting themselves. Fatigue was first noticed at the beginning of the third month of the diet and there was definite evidence of a decrease in minute oxygen consumption per kgm. of body weight.

As the disease progresses, the complexion may become more dingy and somewhat brownish. The gum lesions become more severe. The teeth loosen and fall out and the alveolar processes undergo necrosis. Large bloody effusions may occur, and occasionally there is bloody diarrhea. Hemorrhages into the muscles and deeper tissues give rise to hard, brawny, tender swellings which have been termed "scurvy sclerosis" (Fig. V). Edema of the ankles occurs associated

quickly and complains of breathlessness. The normal degree of alertness is replaced by a disposition to inactivity. There is a loss of appetite and the taking of food is additionally hampered by the painful gums. The latter besides being sore, bleed readily and are found to be congested, spongy, and somewhat hemorrhagic at their edges.



FIG IV GUM CHANGES IN A CASE OF SCURVY

(Fig IV) The normal complexion of the individual may change and become sallow or muddy. Fleeting pains occur in the joints and limbs, especially the legs. Petechiae occur in areas in which capillary pressure is high as in the lower extremities or in regions distal to constricting bands or clothing. These petechiae occur mainly at the site of hair follicles. Ecchymoses may appear most commonly on the lower extremities. Bleeding from the nose is not unusual.

known to increase the requirements for vitamin C, the physical findings characteristic of the scorbutic state, and vitamin C determinations on blood and urine. If a saturation test is used in an effort to measure the degree of the vitamin deficiency it may also serve as a therapeutic test, for if a fairly large dose of ascorbic acid is given, clinical improvement will follow in the physical signs which are due to scurvy.

The average daily intake of vitamin C can be fairly well estimated if the patient is questioned as to the specific food sources of the anti-scorbutic factor in the daily diet. The richest dietary sources, as shown in Table 3, are oranges, lemons, grapefruit, tangerines, tomatoes, fresh strawberries, green peppers, and raw cabbage. It is important in estimating the daily intake of ascorbic acid to determine the amounts of the vitamin C-containing foods that are eaten and the state of such foods when eaten, that is, cooked, canned, or raw, as the treatment of foods will affect their vitamin C content.

The physical findings characteristic of the scorbutic state were described in the previous section. Their intensity will depend on the duration and severity of the deficiency.

As an aid in the diagnosis of vitamin C deficiency many tests have been introduced, some clinical, some laboratory. Before describing and evaluating them, it should be emphasized that the diagnosis of scurvy cannot be made on the basis of any test alone.

Scurvy is accompanied by an increased capillary fragility. The clinical methods used to measure this increase in capillary fragility fall into two general classifications—the positive pressure methods and the negative pressure methods. As an example of a positive pressure method, the Wright modification of the Rumpel-Leed test (177) consists in applying a blood pressure cuff to the arm and keeping it inflated for fifteen minutes, half-way between systolic and diastolic pressures. Five minutes after release of the cuff, the number of petechiae in a 2.5 cm. circle on the flexor surface of the forearm are counted. Wright considers 0–10 normal, 10–20 borderline, and more than 20 abnormal. The Dalldorf test (37) is an example of a negative pressure method. In this test a 1 cm. suction cup is applied to the skin of the upper arm near the deltoid insertion and varying negative pressures are applied for one minute. If petechial hemorrhages are

with a glossiness of the extensor surface of the legs. The skin is usually dry and rough. As the disease progresses these hemorrhages become more extensive and are accompanied in the extremities by edema. Suppuration may develop in any of the hematomas and lead to the formation of huge abscesses. Of 27 cases of scurvy (Table 4) that we studied, 23 showed some gum changes typical of scurvy. Eight of the cases had massive hematomas and 15 had widespread petechiae. Death may occur as a result of infection or hemorrhage.

Anemia of a variable degree occurs in a certain percentage of adults with scurvy. In adult scurvy one may expect to find in about 33 per cent of the cases red blood cell counts between 2 and 3 million per cu mm, in about the same percentage counts between 3 and 4 million per cu mm, and in the remainder a slight anemia, or none (107). Moderate central pallor of the cells is frequent. If hemorrhage has been an important factor in the production of the patient's anemia, a greater degree of achromia and a lower color index will occur. The cause of the anemia in scurvy, although in part due to undernutrition, intercurrent infection, and hemorrhage, is according to some (107) in the main dependent on an insufficient red blood cell production resulting from inadequate function of the bone marrow as a result of a chronic lack of vitamin C. The blood platelets occur in from normal to moderately increased amounts. The leucocytes in uncomplicated cases are usually between 4,000 and 6,000 per cu mm. The pattern is not much disturbed, although a slight lymphocytosis is often observed.

Scurvy interferes with the healing of wounds (96, 175) and lowers the patient's resistance to superimposed infections of all sorts. Scurvy is often accompanied by symptoms of other deficiency diseases (181, 38) and is seldom uncomplicated. Of 22 cases of scurvy reported by Ralli and Friedman (128) only 6 were uncomplicated by other diseases. The associated conditions included arteriosclerosis, diabetes, syphilis, tuberculosis, arthritis, hyperthyroidism, and alcoholism.

#### DIAGNOSIS

The criteria for the diagnosis of scurvy are a history of the dietary inadequacy of vitamin C or the presence of some condition that is

34	I	52	21 mo <sup>3</sup>	I uc's and arthritis	0	+	0	0	+	0	No	No	Both arms	> 1,500
35	I	53	Undetermined	Hypothyroid	0	0	0	0	0	0	No	No	Lower arms	
36	M	70	On and off for three years	Art scl and hypertension	0	0	0	+	+	-	No	No		
37	F	49	3-4 mo <sup>1</sup>	Fibromyoma of uterus	0	0	0	0	Slt	0	No	No	Colored patient	
38	M	41	24 mo <sup>1</sup>	Aneurysm of aorta	0	-	0	0	0	0	No	No	Both arms	> 6,700
39	I	47	Always poor	Diabetes and thrombophlebitis	0	+	0	0	0	0	No	No	Arms, legs, face	
40	M	45	2 years	Coronary occlusion	0	+	1	1	+	0	No	No	Both arms	> 6,700
41	F	45	5 years	None	+	-	0	0	Slt	0	No	No	No	8,600
42	M	55	Several years	I uc's	+	1	-	-	-	0	No	No	Legs and forearms	> 23,300
43	M	71	12 mo <sup>1</sup>	Art scl, osteoarthritis, malnutrition	-	1	-	-	0	0	No	No	No	14,400
44	M	62	3 mo <sup>1</sup>	Malnutrition	-	1	1	1	1	-	No	No	No	a > 8,600 b > 4,400
45	M	72	2 years	Art scl, beri beri, chronic cholecystitis	0	0	0	0	-	0	No	No	Thigh	> 2,300
46	M	69	Dietary history unreliable	Chronic alcoholism, I uc's, art scl	-	-	0	0	0	0	No	No	Legs	> 11,000



TABLE 4

Summary of Patients with Scurvy

Summary of Patients with Scurvy

CASE NO	SEX	AGE	DURATION OF DEFICIENCY	OTHER COMPLICATIONS	CLINICAL SIGNS OF VITAMIN C DEFICIENCY						AMOUNT OF VITAMIN C NECESSARY TO SATURATE		
					Refractive to the gums				Other clinical signs				
					Spongy	Piled up	Bleeding	Ulcerated	Hem. into gums and buccal membrane	Massive subcutaneous hemorrhage		Presence of petechiae	Location
20	M	40	3-4 mos	None	+	+	+	+	+	Massive	Into both legs	No	mg
21	M	68	12 mos	Art scl and hypertension	0	0	0	+	+	+	Both legs	Left leg	6,100
22	F	38	3 mos	None	0	0	+	+	0	0	No	No	>4,000
23	F	22	3 mos	Malnutrition	+	+	+	+	0	0	No	No	>2,500
24	M	55	14 mos	None	+	+	+	0	0	0	Both legs and popliteal spaces	No	2,700
25	M	21	14 mos	Possible rh fever	0	+	0	0	+	0	No	No	>2,000
26	F	76	12 mos	Art scl	0	0	0	0	0	0	No	Legs and forearms	>2,600
27	F	45	11 mos	Ulcer diet	0	+	+	+	0	0	No	No	6,660
28	F	21	12 mos	None	0	+	+	+	0	0	No	No	1,700
29	M	60	3 mos	Strept hem	0	0	0	0	0	0	No	Both legs	>800
30	M	71	24 mos	Tuberculosis	0	+	+	+	0	0	No	Bleeding lips	>1,200
31	M	70	Intermittent for three years	None	0	+	0	+	+	+	No	Both legs	6,700
32	M	56	12 mo,	Alcoholism	0	0	+	0	0	0	No	Epistaxis	5,900
33	F	42	4 mos	Profound malnutrition	0	0	0	0	0	0	No	Lipstaxis	

34	1	52	21 mo.	I us. and urthrit.	0	-	0	-	0	No	No	Both arms	> 1,500
35	1	54	Undetermined	Hypertrophy rod	0	0	0	0	0	No	No	Lower arms	
36	M	70	On and off for three years	Art scl and hypotension	0	0	+	-	-	No	No		
37	f	49	3 4 mo.	I bromyama of uterus	0	0	0	Slt	0	No	No	Colored patient	> 6,700
38	M	44	24 mo.	Aneurysm of tort.	0	-	0	0	0	No	No	Both arms	
39	f	47	Always poor	Diabetes and thrombo phlebitis	0	+	0	0	0	I mgs. purpura spots	I mgs. purpura spots	Arms, legs, face	
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41	f	45	5 yrs	None	1-	-	0	Slt	0	No	No	No	8,600
42	M	55	Several years	Lues	1	-	-	-	0	No	No	Legs and forearms	> 23,300
43	M	71	12 yrs	Art scl, osteoarthritis, malnutrition	-	1-	1-	0	0	Larg. purpura spots	Larg. purpura spots	No	14,400
44	M	62	3 mo.	Malnutrition	1	-	1	1	-	Around and into joints	Around and into knee joints	No	a > 8,600 b > 4,400
45	M	72	2 years	Art scl, beri beri, chronic cholecystitis	0	0	0	+	0	Purpura	Purpura	Thigh	> 2,300
46	M	69	Dictary history unchangeable	Chronic alcoholism, lues, art scl	-	+	0	0	0	Bechymous over arms	Bechymous over arms	Legs	> 11,000

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Summary of Patients with Scurvy

Case No	Sex	Age	Duration of Deficiency Diet	Other Complications	Clinical Signs of Vitamin C Deficiency							Amount of Vitamin C Necessary to Saturate
					Refractory to the 1 gm				Other clinical signs			
					Spongy	Pilled up	Bleeding	Ulcerated	Hem. into gums and buccal membrane	Massive subcutaneous hemorrhage	Presence of petechiae Location	
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23	F	22	3 mos	Malnutrition	+	+	+	0	0	No	No	2,700
24	M	55	14 mos	None	+	+	+	0	0	Both legs and popliteal spaces	No	>2,000
25	M	21	14 mos	Possible rh fever	0	+	0	0	+	No	No	>2,600
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27	F	45	11 mos	Ulcer duct	0	+	+	0	0	No	No	6,660
28	F	21	12 mos	None	0	+	+	0	0	No	No	1,700
29	M	60	3 mos	Strept hem	0	0	0	0	0	No	Both legs	>800
30	M	71	24 mos	Tuberculosis	0	+	0	0	0	No	Bleeding lips	>1,200
31	M	70	Intermittent for three yrs	None	0	+	0	+	+	No	Both legs	6,700
32	M	56	12 mos	Alcoholism	0	0	+	0	0	No	Epistaxis	
33	F	42	4 mos	Profound malnutrition	0	0	0	0	0	No	Epistaxis	5,900

This increase in the plasma concentration of the vitamin following a standard dose will be conditioned by the extent to which the tissues have been depleted of their storage of vitamin C. We have therefore an indirect measure of the degree of tissue desaturation. In the scorbutic patient, because of the extreme degree of tissue unsaturation, the urinary excretion following a test dose of 100 to 500 mg of vitamin

TABLE 5\*

*Mg of Vitamin C Excreted in 3 and 21 Hours on Diet and Following Injection of 100 mg of Ascorbic Acid in Normal, Subnormal and Scorbutic Subjects*

NORMALS				SUBNUTRITION CASES				CASES WITH SCURVY			
Mg excreted on diet		Mg excreted after test dose		Mg excreted on diet		Mg excreted after test dose		Mg excreted on admission		Mg excreted after test dose	
3 hours	21 hours	3 hours	21 hours	3 hours	21 hours	3 hours	21 hours	3 hours	21 hours	3 hours	21 hours
25.4	180.7	52.7	125.8	1.4	9.5	11.5	4.8	3.3		3.6	
9.0	53.2	24.2	87.1	2.2	11.7	5.6	1.6	2.2		1.3	4.7
16.8	81.6	81.8	73.8	2.3	9.5	14.2	9.1	Not done		7.9†	
21.2	44.7	67.0	89.3					2.1	8.2	3.9	12.9
8.5	109.0	40.5	104.0					No Vitamin C Titrable			
6.4	31.1	32.0	34.6					2.0	6.2	Tr	0
10.9	36.1	57.8	65.7					0.7	1.5	0.3	2.8
12.9	30.1	44.6	49.3					0.3	0	1.0	0
4.9	39.7	43.5	25.1					0.2	20.9‡	9.7†	23.9
4.5	58.9	47.8	53.5					2.0	17.2§	4.7	14.1
12.1	51.9	37.6	47.9					0	0.75	1.8	21.5
10.9	86.9	34.4	80.9					0	0	0.4	1.5
								0.69	5.2	2.3	6.6

\* Reprinted from Proc. Exp. Biol. and Med. An Excretory Test for Vitamin C Deficiency and Subnutrition. By Elaine P. Ralli, Gerald J. Friedman, and Murray Kaslow. Proc. Soc. Exp. Biol. and Med., 36, p. 52, 1937.

† Clinic patient had been taking some orange juice for week prior to test.

‡ Clinic patient had been taking orange juice for one week.

§ Patient received 100 mg. Cevitamic Acid after the 3-hour excretion.

C is small. We have studied (129) the effect on the urinary excretion of 100 mg doses of vitamin C given intravenously in a group of normal, subnormal, and scorbutic subjects (Table 5). The normal subjects excreted 50 per cent of the injected vitamin within three hours. The subjects on diets low in vitamin C excreted about 15 per cent in this period and the scorbutic subjects excreted less than 5 per cent of the vitamin. 22 patients with scurvy were treated

produced at 25 cm negative pressure or below, the capillary fragility is regarded as abnormal. It is generally accepted now that all these capillary fragility tests are of little value in diagnosing vitamin C deficiency (4, 99, 33).

The intradermal test (136, 123) in which the dye, dichlorophenolindophenol, is injected into the skin, and the length of time necessary for the disappearance of color timed, has been shown to be of no value (130, 61).

In 1935 Abbassy, Harris, Ray and Marrack (1) introduced the determination of the 24-hour urinary excretion of the vitamin as an index of the vitamin C status. With the recent advances in our knowledge of the excretion of the vitamin, it has become evident that the 24-hour excretion of the vitamin is a poor index of vitamin C deficiency, but does reflect the intake in a saturated individual. For example, Ralli et al (125) found that an excretion of 6 to 14 mg daily occurs at intakes varying from 50 to 100 mg of vitamin C daily and at fasting plasma levels ranging from 0.3 to 1.0 mg per cent. This is explained by the fact that in the unsaturated individual about 99 per cent of the vitamin presented to the kidney is reabsorbed. On the other hand, once saturation has been obtained, all the excess of the vitamin ingested above that which can be utilized is excreted, since the kidney is maximally limited in its reabsorption of ascorbic acid. Although the 24-hour excretion is not a measure of vitamin C deficiency, in clinical scurvy there is no vitamin C in the urine. The traces occasionally reported are probably due to non-vitamin C-reducing substances.

A better picture of vitamin C nutrition is obtained by the use of test or saturation doses of the vitamin than by the determination of the 24-hour excretion. The 'test dose method' consists in either the oral or intravenous administration of a given amount of vitamin C and the determination of the amount excreted within a given period following the administration. Probably the best way of administering the vitamin is intravenously, as this obviates any error due to lack of absorption. From all the reports published (129, 71) most of the vitamin that is to be excreted will appear in the urine within three hours. Naturally the amount excreted will depend partly on the extent to which the plasma concentration of vitamin C is raised.

(3, 5, 62) This is a more accurate index of the state of vitamin C nutrition than is the 24-hour urinary excretion and it is simpler than the test dose. Abt and Farmer (4) have stated that a plasma concentration of vitamin C above 0.7 mg per cent indicates a normal state of vitamin C nutrition. Plasma levels ranging from 0.7 to 0.5 mg per cent were interpreted as indicating a state of vitamin C subnutrition, and plasma levels below 0.5 mg per cent were considered as the "scurvy level." All observers agree that plasma levels of vitamin C of 0.7 mg per cent or above indicate a satisfactory state of vitamin C nutrition but the more recent observations indicate that low plasma concentrations of ascorbic acid *do not* of themselves provide a reliable index either of vitamin C deficiency or the degree of tissue unsaturation (33, 21). We have observed several subjects on a daily intake of 50 mg of ascorbic acid (125) and found in every case that this dose will only maintain the plasma concentration of vitamin C at about 0.4 mg per cent. Complete deprivation of the vitamin following this daily dose was followed by a rapid drop of the plasma concentration of vitamin C to zero without the occurrence of any symptoms of scurvy. Thus although the scorbutic patient will have no vitamin C in his plasma one may also find subjects with no clinical evidences of scurvy in whose plasma there is no ascorbic acid. Obviously then, the absence of ascorbic acid from the plasma is not of itself diagnostic of the degree of vitamin C deficiency. The most accurate index of vitamin C deficiency, according to Butler and Cushman (21) is the level of vitamin C in the white-cell-platelet layer. They found that the level of vitamin C in the white-cell-platelet layer might be within normal limits (25 to 38 mg vitamin C per 100 grams white blood cells) in spite of a low plasma level of the vitamin. They also reported that the whole blood will reflect the state of vitamin C nutrition more accurately than the plasma, as the cellular elements of the blood may still contain the vitamin when there is none left in the plasma. Crandon, Lund, and Dill (33) determined the vitamin C levels of the plasma, whole blood, and the white-cell-platelet layer in a normal subject kept on a vitamin C-deficient diet. The plasma ascorbic acid fell to zero after 41 days of the diet, the whole blood ascorbic acid reached zero after 124 days of the diet. The first clinical signs of scurvy appeared on the 134th day of the diet, 10

by feeding crystalline vitamin C and the intravenous test doses were repeated at intervals during the course of treatment. The amount of vitamin C excreted in the 3 hour period following the injection of a 100 mg test dose was found to increase as the patient became saturated with the vitamin. In this respect it served as an index of the state of vitamin C nutrition. An example of the response to such a test dose and its relation to the total amount of vitamin C ingested

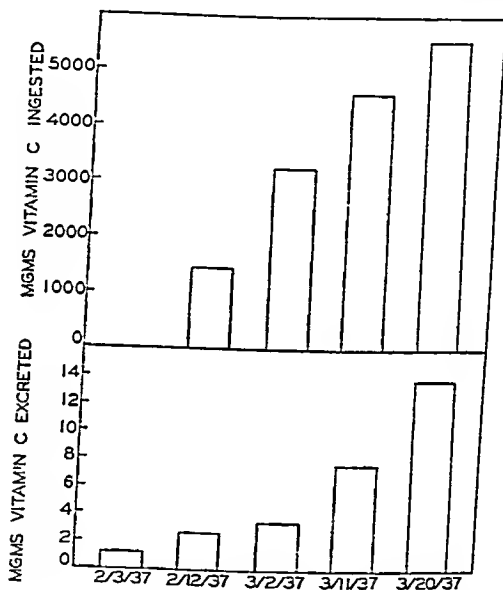


CHART 1 THE THREE HOUR EXCRETION TESTS AFTER 100 MG OF VITAMIN C ADMINISTERED INTRAVENOUSLY, BEFORE AND AFTER THE DAILY ADMINISTRATION OF VITAMIN C IN A CASE OF SCURVY (CASE 39)

Reprinted from *Ann Int Med.*, 11, 1938, by Elaine P Ralli, F A.C.P., and Gerald J Friedman

is shown in Chart 1. This patient was a 47 year old female with diabetes and thrombophlebitis, which had followed the appearance of large ecchymoses. Areas of purpura and petechiae were present over both extremities. The gums were piled up and spongy. The plasma concentration of vitamin C determined by the Farmer and Abt method (49) was 0.1 mg per cent.

In recent years the determination of the fasting plasma ascorbic acid concentration has been used as a measure of vitamin C nutrition.

clinical signs of scurvy, the diagnosis of *the prescorbutic state* is warranted, by which we mean the state during which the clinical signs of scurvy may appear. The exact time of the appearance of the physical signs under these circumstances may vary in different individuals, but it will apparently not be many days and will probably depend on the age of the subject, the presence of any intercurrent infection, and the physical stress of the subject's life. Until the physical signs do appear, the symptoms will probably be general, such as fatigue and weakness.

#### THErapy

That the administration of ascorbic acid leads to a rapid and dramatic cure of the scorbutic state has been well established. Vitamin C may be administered in the form of foods (the citrus fruit juices being the most commonly used) (Table 3) or in the crystalline form. The latter may be given orally, intramuscularly, or intravenously. No toxic effects have been ascribed to it, and we have given as much as 6 grams intravenously in one dose on several occasions, and have also maintained plasma concentrations of 25 mg per cent for 1 to 2 hours without observing any untoward results (126). Some investigators (137, 171) have described idiosyncracies to crystalline ascorbic acid in children.

In the treatment of scurvy two facts are outstanding, first, that relatively small doses of the vitamin will clear up the physical signs and second, that large amounts are needed to saturate the tissues and that the amounts required may vary considerably in different individuals. For example Schultzer (142) reports that 9.5, 7.0, and 14.4 grams of the vitamin were needed to saturate three of the patients that he studied, but on the other hand another of his patients was cured of the signs of scurvy when given 40 mg of vitamin C intravenously daily for 2 weeks (141, 143). The amounts of vitamin C necessary to return the scorbutic patients whom we studied to a normal state of vitamin C nutrition are shown in Table 4. These observations also support those of other investigators who found that the amounts of ascorbic acid necessary to saturate the tissues vary in different individuals depending on the degree of the deficiency and its duration. We have furthermore observed that the total amount of vitamin C



days after there was no ascorbic acid in the white-cell-platelet layer. Thus, of all the blood elements examined, the white-cell-platelet ascorbic acid was the last to be depleted and they noted, the first to become saturated following vitamin C therapy. This fact was also noted by Butler and Cushman (21) in several cases of scurvy treated with vitamin C. The methods used for determining vitamin C in the white-cell-platelet layer and in whole blood are both tedious and difficult and will probably not be adaptable for routine laboratory use.

The dietary inadequacy of vitamin C in the case reported by Crandon covered a period of about four months before clinical signs of scurvy appeared. This is interesting in view of the fact that scurvy did not become a menace to mariners until long sea trips were undertaken. As mentioned before, the clinical signs of scurvy may appear sooner if infection or some other pathological state supervenes.

It becomes apparent then, that the whole blood, the plasma, the white-blood-cell platelet layer and the urine may all be devoid of vitamin C without clinical signs of scurvy being present. In the absence of characteristic signs the clinical diagnosis of scurvy, solely on the basis of chemical determinations, is not warranted. However in normal subjects vitamin C is present in the white blood cells and the plasma and therefore its complete absence, particularly from the white-cell-platelet layer cannot be considered 'normal'. On the basis of our present knowledge it is not known what less obvious pathological effects may result from such a depletion of the plasma or cellular elements of the blood prior to the appearance of the diagnostic signs of scurvy. From the one case thus far reported (33) on a vitamin C-deficient diet, the physical signs of scurvy did not occur until the blood plasma had contained no vitamin C for 93 days and the white-cell-platelet level had been zero for 10 days. Apparently then, the white-cell-platelet level of vitamin C is the most sensitive index of the state of vitamin C nutrition. It is equally clear that when there is no vitamin C in the plasma one is approaching a depleted state of vitamin C in the body and one which, if continued, will lead to the appearance of the clinical signs of scurvy. We suggest on the basis of these studies that when the plasma vitamin C is zero the diagnosis of *vitamin C deficiency* is warranted. When the white-cell-platelet level of vitamin C is zero, even if there are no

duration His mother and sister had died of tuberculosis He had pneumonia at 17 and a chancre at 21 The latter was treated by munc-

TABLE 6

*Diet*

	CARBOHY- DRATE	PROTEIN	FAT	VITAMIN C
Breakfast				
30 grams cereal				0
2 eggs				0
60 grams bread				0
240 grams milk				0 24
10 grams butter				0
20 grams sugar				0
Coffee				0
	88	20	30	
Lunch				
150 grams meat (medium fat)				4
150 grams rice or spaghetti (plain)				0
480 grams milk				0 48
120 grams bread				0
10 grams butter				0
1 custard				0
Tea, with 10 grams sugar				0
	143	53	68	
Supper				
60 grams cheese or 3 eggs				0
150 grams rice or spaghetti (plain)				0
240 grams milk				0 24
120 grams bread				0
10 grams butter				0
1 jello				0
Tea, with 10 grams sugar				0
	121	27	40	
Total	352	100	138	5

tions and later by intravenous and intramuscular injections The patient had been a kitchen worker for all of the 45 years he had been in America

necessary to saturate the tissues in a scorbutic subject will depend on the method of administration of the vitamin. For example, if small daily doses are given, the total quantity necessary to saturate the tissues is greater than if larger doses are given. This is due to the fact that the body will normally utilize as much as 100 mgm daily. Therefore, to secure saturation a much larger daily dose should be used. This is demonstrated in some of the cases discussed later.

In order to clarify further the requirements of vitamin C in scurvy, we have studied in detail 5 patients with the clinical signs of scurvy. The procedure was similar to that used in a previous study on the requirement for vitamin C in the normal adult (125). In that study it was established that the optimal requirement of vitamin C in a normal adult was 100 mg daily, this being the smallest daily dose on which saturation of the body tissues was attained and maintained. The scorbutic patients in this study were hospitalized and fed diets adequate in all respects except for vitamin C, which was present in minimal amounts, that is, less than 5 mg daily (Table 6). The 24-hour urinary excretion of vitamin C was determined daily during the entire period of observation. The urines were collected in dark bottles, to which was added enough 5N sulphuric acid containing 1 per cent of 0.1 M hydroxyquinoline, so that by the end of 24 hours the concentration of acid was approximately 10 per cent by volume. The urinary volume was remarkably constant in each individual from day to day so that the amount of acid necessary was readily calculated. The bottles were kept in the icebox and the urines added when voided. The plasma concentration was determined two to three times weekly. The determinations for blood and urine were done in the photoelectric colorimeter using the methods described by Mindlin and Butler for blood plasma (109) and by Evelyn et al for urine (48). Complete blood counts and hemoglobin determinations were carried out on 3 of the cases during periods when the subject was receiving vitamin C in crystalline form and during a period when he received no vitamin C and was on a diet deficient in the vitamin. The studies on these 5 cases of scurvy and the summaries of their courses are as follows.

*Case #42* was a 55-year old single white male, born in Czechoslovakia. He entered the hospital on December 19, 1938, complaining of a purpuric rash on both legs and arms and swelling of his hands and feet, of 5 days'

duration His mother and sister had died of tuberculosis He had pneumonia at 17 and a chancre at 21 The latter was treated by inunc-

TABLE 6

*D et*

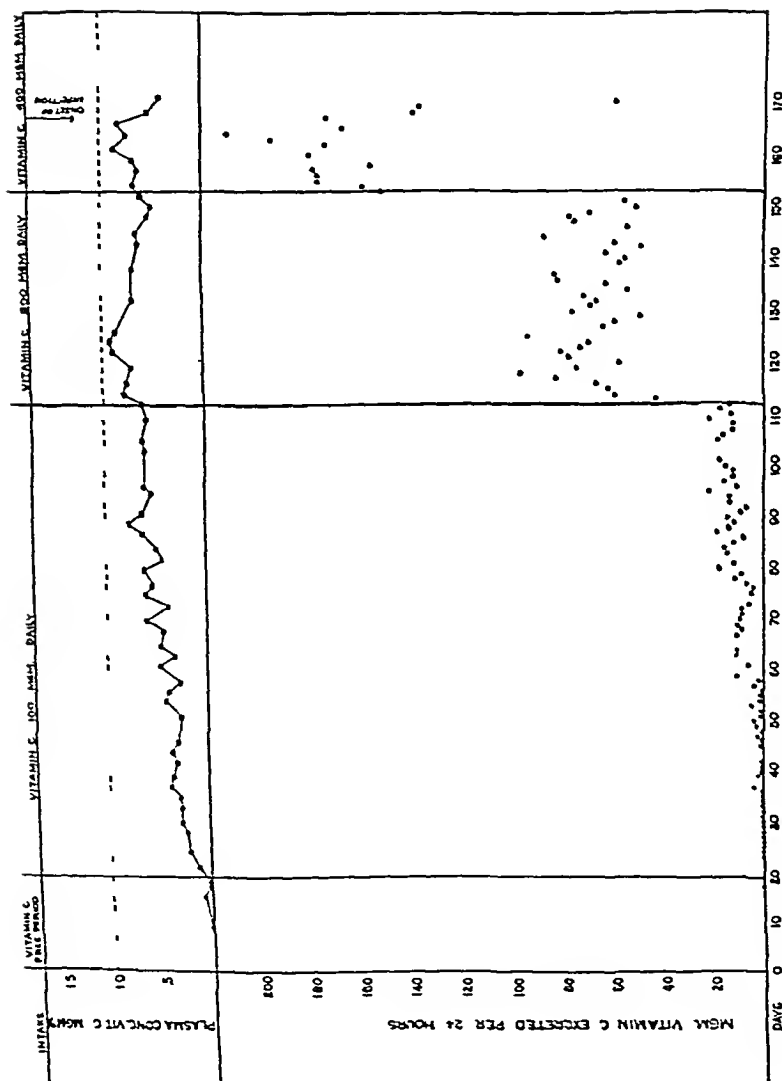
	CARBOHY- DRATE	PROTEIN	FAT	VITAMIN C
Breakfast				
30 grams cereal				0
2 eggs				0
60 grams bread				0
240 grams milk				0 24
10 grams butter				0
20 grams sugar				0
Coffee				0
	SS	20	30	
Lunch				
150 grams meat (medium fat)				4
150 grams rice or spaghetti (plain)				0
480 grams milk				0 48
120 grams bread				0
10 grams butter				0
1 custard				0
Tea, with 10 grams sugar				0
	143	53	68	
Supper				
60 grams cheese or 3 eggs				0
150 grams rice or spaghetti (plain)				0
240 grams milk				0 24
120 grams bread				0
10 grams butter				0
1 jello				0
Tea, with 10 grams sugar				0
	121	27	40	
Total	352	100	138	5

tions and later by intravenous and intramuscular injections The patient had been a kitchen worker for all of the 45 years he had been in America.

His diet was grossly inadequate in fresh fruits, vegetables, meat and milk. It consisted mainly of white bread, rolls, and coffee. The present illness, which began five days prior to admission with swelling of the hands and feet, was not accompanied by dyspnea or any signs of cardiac distress. There was no pain or itching accompanying the rash. The patient appeared well nourished and not acutely ill. There were no conjunctival hemorrhages, and the eye and ear examination was normal. The tongue was smooth and glossy. Many teeth were missing and the remaining ones were carious. The gums were piled up, ulcerated, and spongy. The mucous membranes were normal. The tonsils were enlarged and boggy but not reddened. There was no adenopathy. There were a few scattered râles throughout both lungs, which were otherwise normal. The heart was slightly enlarged, the sounds were normal, and the rhythm was regular. The blood pressure was 178/108. The abdomen was negative. Over the anterior and posterior aspects of both forearms from the wrists to the elbows there was a purpuric rash. There were no pustules or surrounding zones of erythema. The purpuric spots were discrete and varied in size. There was a similar rash on the lower extremities and some spots on the thighs. There was edema of both hands to the wrists, of the ankles, and lower legs. The edematous areas were painful on pressure. The deep reflexes were equal and active. There were no pathological reflexes and no calf muscle tenderness or solar hyperesthesia.

The laboratory data were as follows: Temperature 100.6°F, R B C 4.8 million, Hgb 88 percent, W B C 9,500, adult polymorphonuclear cells, 75 percent, Meta II, 6 percent, lymphocytes, 10 percent, mononuclears, 6 percent, eosinophiles, 2 percent, platelets, 217,000. The Wasserman reaction was 4 plus. Non-protein nitrogen, 32 mg percent, blood sugar, 75 mg percent. The urea clearance was 81 percent of normal. The Rumpel-Leed test was negative. X-ray of the heart showed moderate enlargement in all diameters with accentuation of the left ventricular curve and minimal widening of the aortic arch. The electrocardiogram was normal.

*Course* The purpura began to fade within a few days after admission but new crops of petechiae replaced these. The plasma ascorbic acid determinations on four different occasions prior to the institution of specific therapy showed absolutely none in the plasma. There was no vitamin C found in the urine. In view of the history, the physical findings, and the absence of vitamin C in the plasma and urine, the diagnosis of scurvy was made. The studies on this patient are shown in Chart 2. He was observed for a period of 170 days. During the first period of 19 days on a diet



CASE NO 42

CHART 2 THE EFFECT OF FEEDING 100 MG OF VITAMIN C DAILY TO A PATIENT WITH SCURVY

On admission this patient had ulcerated, spongy gums, purpuric spots over the elbows and over the lower extremities and thighs. Although the feeding of 100 mg of vitamin C daily failed to raise the plasma level of vitamin C to the same extent that it would have in a normal subject, the clinical signs improved rapidly and the petechiae disappeared. When the daily dose of vitamin C was raised to 200 mg the plasma vitamin C rose but the patient retained about 132 mg which is about 40 mg more than a normal subject would retain. After 40 days the daily intake was raised to 400 mg. The patient retained about 225 mg of this. 15 days later the patient developed an infection and in spite of such a large daily dose there was a prompt fall in the plasma level and the excretion dropped.

devoid of vitamin C, the urine and blood ascorbic acid remained zero. The clinical signs were about the same as on admission. The patient was then fed 100 mg of crystalline ascorbic acid (Merck) daily in two doses of 50 mg each for the next 93 days. The clinical symptoms of scurvy improved rapidly and the hemorrhagic spots disappeared. The gum changes receded more slowly. The fasting plasma ascorbic acid concentration rose slowly and finally leveled off at about 0.57 mg percent. For the first 30 days the urinary excretion of vitamin C averaged 1.2 mg per day, during the second 30 days, 9.5 mg, and for the last part of the period, 14.7 mg of ascorbic acid was excreted daily. The average for the 93 days was 7.7 mg of vitamin C daily, so that about 92 mg was retained daily. In the next period of 40 days the patient was fed 200 mg of vitamin C daily. The retention rose to 132 mg daily. The plasma ascorbic acid averaged 0.73 mg percent. The daily intake was then increased to 400 mg. The urinary excretion rose to an average of 17.5 mg daily, so that about 225 mg was retained daily. The studies were interrupted 15 days later when the patient developed acute appendicitis. On the day before the symptoms appeared, the plasma ascorbic acid was 0.82 mg percent and the urinary excretion, 17.2 mg. The day the infection manifested itself the plasma ascorbic acid fell to 0.52 mg percent and the excretion fell to 13.7 mg. The second day of the infection, the excretion was 13.5 mg and on the third day, 57.5 mg, at which time the plasma level of the ascorbic acid had fallen to 0.40 mg percent.

Prior to the onset of the infection the patient was fed a total of 23,300 mg of vitamin C over a period of 151 days, and he still was retaining a much larger quantity than a normal individual would have retained. The rapid fall in the ascorbic acid content of the plasma, accompanied by the decrease in the urinary excretion which occurred with the onset of the acute infection, is an index of the increased requirement for vitamin C in the presence of infection, and is additional evidence that the clinical symptoms of scurvy may be precipitated by an infectious process. This case also demonstrates the fact that when the ascorbic acid is administered in moderate daily doses the total amount necessary to raise the state of vitamin C nutrition to normal is greater than if large doses are given in a single dose.

Case #43 was a single, American male, 71 years of age. He entered the hospital on March 21, 1939, because of inability to walk, due to back pain. The family history was negative. His past history included amputation of the right leg in 1935 due to gangrene as a result of frost-bite. His diet had been deficient in quality and quantity for several years. He stated

that he had had no fresh fruit for the past year and rarely ate fresh vegetables. For the past six months he had noticed weakness, some loss of weight, and pain across the lower back. His appetite, which had been poor for some time, had gone completely in the past three days. He had noticed purple spots on his skin during the past two months. On examination, he was undernourished. He was not dyspneic or cyanotic. There was corneal opacity and an iridectomy of the left eye. There was a pterygium of the right cornea. The right pupil was small and irregular but reacted to light and accommodation. The conjunctivae were pale. In the mouth the teeth were carious and decayed. The gums were spongy and heaped up. The tongue was normal. There was no adenopathy. The lungs were clear. The heart was not enlarged, the sounds were of fair quality. The rhythm was regular and there were no murmurs. The blood pressure was 134/80. The liver and spleen were not felt. There was a mid-thigh amputation of the right leg. Along the outer aspect of the left thigh there was a punctate purplish area. Several purpuric spots were seen on the left hand and over the right hand. There was no edema. Extension of both elbow joints was limited. Motion of the sacro-lumbar spine was painful. The reflexes were hyperactive.

*Laboratory data.* The temperature was normal. R.B.C. 2.86 million; Hbg. 49 percent (7.14 grams), color index, 0.9, platelets, 481,600, W.B.C. 8,250 polymorphonuclears 63 percent, lymphocytes, 26 percent, mononuclears, 4 percent, eosinophiles, 2 percent, basophiles, 1 percent. The red cells showed slight changes in size and shape, and some polychromatophilia. The urine examination was negative. The Rumpel-Leed test was negative. The Wasserman was negative. Non-protein nitrogen, 33 mg percent. Blood sugar, 100 mg percent. X-ray of the extremities showed advanced sclerosis of the blood vessels. All the bones showed a moderate amount of demineralization. The heart showed minimal enlargement in all diameters and accentuation of the left ventricular curve. The aorta was tortuous, elongated, and sclerotic, with calcific plaques in the aortic knob. There were diffuse fibrotic and emphysematous changes throughout both lungs. There were hypertrophic osteoarthritic changes of the elbow joints. Two determinations of the plasma ascorbic acid prior to therapy revealed none. There were traces of vitamin C in the 24-hour urine.

Because of the dietary history, the gum changes, the ecchymoses, and the absence of ascorbic acid in the plasma, the diagnosis of scurvy was made. With the onset of vitamin C therapy the patient's physical condition improved rapidly and within a week almost all the hemorrhagic spots



had disappeared. The anemia, however, improved slowly, and only after four months in the hospital did the red blood cell count reach 4.1 million and the hemoglobin then rose to 80 percent.

The vitamin C requirement of this scorbutic patient was studied over a period of four months. For the first four days he was kept on the vitamin C-free diet. During this time there was no ascorbic acid in the plasma and the urinary excretion averaged 1.7 mg per 24 hours (Chart 3). The patient was given intravenously in 1000 mg doses a total of 4000 mg of vitamin C. These were given at intervals of one hour. This dose would saturate the tissues of any normal person. The plasma concentration was 4.56 mg percent after the first dose, 11.5 mg percent after the second dose, and after the third dose it rose to 12.9 mg percent. In the 24 hours following the injections, 1668 mg of ascorbic acid was excreted. Of this amount, 1290 mg appeared in the first five hours. The next morning the plasma vitamin C had fallen to 1.14 mg percent. For the next 52 days the patient was fed 200 mg of vitamin C daily in 50 mg doses. A normal subject fed this amount daily would have excreted about 100 mg daily. The daily urinary excretion of vitamin C in this case was 49 mg. The plasma concentration averaged 1.44 mg percent. The patient was retaining about 151 mg of vitamin C daily and this amount was capable of maintaining a normal plasma concentration. The vitamin C intake was then reduced to 150 mg daily. On this intake the fasting plasma concentration of vitamin C averaged 1.08 mg percent, and the 24-hour urinary excretion averaged 49 mg. This indicated that the tissue stores were about saturated as the patient was now retaining only about 101 mg daily. To check this, the intake was raised again to 200 mg daily and this was accompanied by an increased excretion, 96 mg daily, the retention remaining at a little above 100 mg, actually about 104 mg daily. The plasma vitamin C averaged 1.16 mg percent. The daily intake of vitamin C was then reduced to 100 mg daily. The excretion fell rapidly to an average of 4.8 mg, which indicated an average retention of 95 mg of vitamin C daily. The plasma level averaged 1.18 mg percent. The patient, as far as his requirement for vitamin C was concerned, was behaving as a normal individual whose tissue stores are saturated with the vitamin. This case illustrates the effect of massive therapy in a scorbutic patient in an effort to produce saturation of the tissue stores of vitamin C. It shows that even after such massive doses the scorbutic subject will require for a period of time more vitamin C daily to maintain a normal level of vitamin C in the plasma than will the non-scorbutic subject. In the period of 52 days in which this patient was utilizing increased amounts

of the vitamin, 14,400 mg. of vitamin C was fed, and of this 4,220 mg was excreted, resulting in a retention and utilization of 10,180 mg of vitamin C

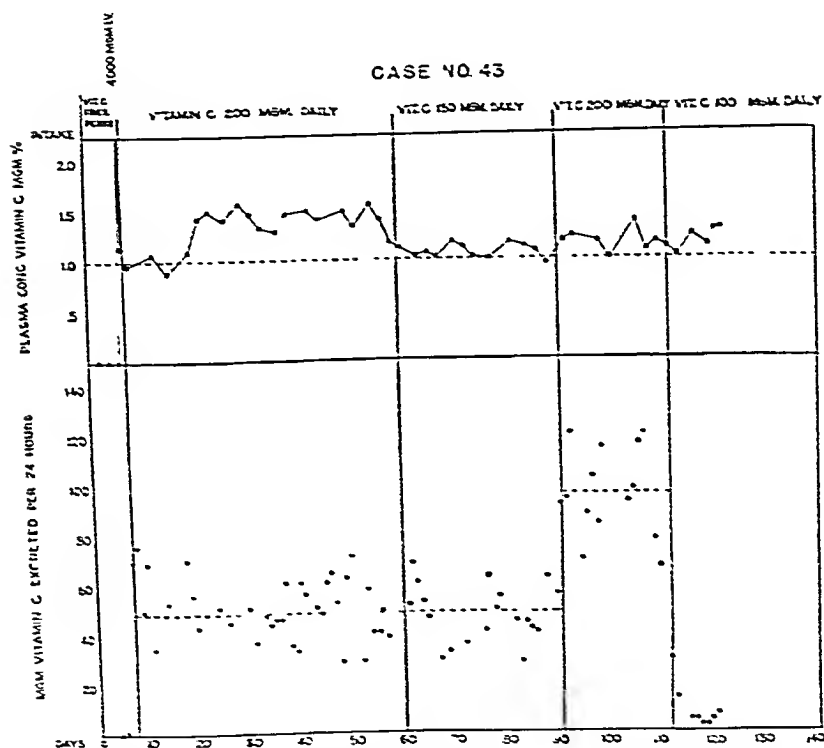


CHART 3. THIS PATIENT WAS ADMITTED WITH THE CLINICAL SIGNS OF SCURVY, INCLUDING GUM CHANGES, PETECHIAE, AND PURPURIC SPOTS

At the point indicated on the chart he was given 4,000 mg of vitamin C intravenously in 1,000 mg doses, at hourly intervals. Following this he was kept on 200 mg of vitamin C daily by mouth. The plasma vitamin C remained elevated during this period and urinary excretion averaged 49 mg daily. After 52 days the vitamin C intake was reduced to 150 mg daily. The plasma level fell but remained at the normal level. The daily excretion averaged 49 mg. In the next period the intake of vitamin C was raised to 200 mg daily and this was accompanied by a rise in the excretion of vitamin C and a slight rise in the plasma concentration. This rise in excretion demonstrated that the patient's tissues were saturated, and this was substantiated by the fact that in the last period when the vitamin C intake was reduced to 100 mg daily the plasma level remained normal, and the excretion fell to within the normal range.

When this scorbutic patient's tissue stores had become saturated with vitamin C he retained the same amount of vitamin C daily as would a normal

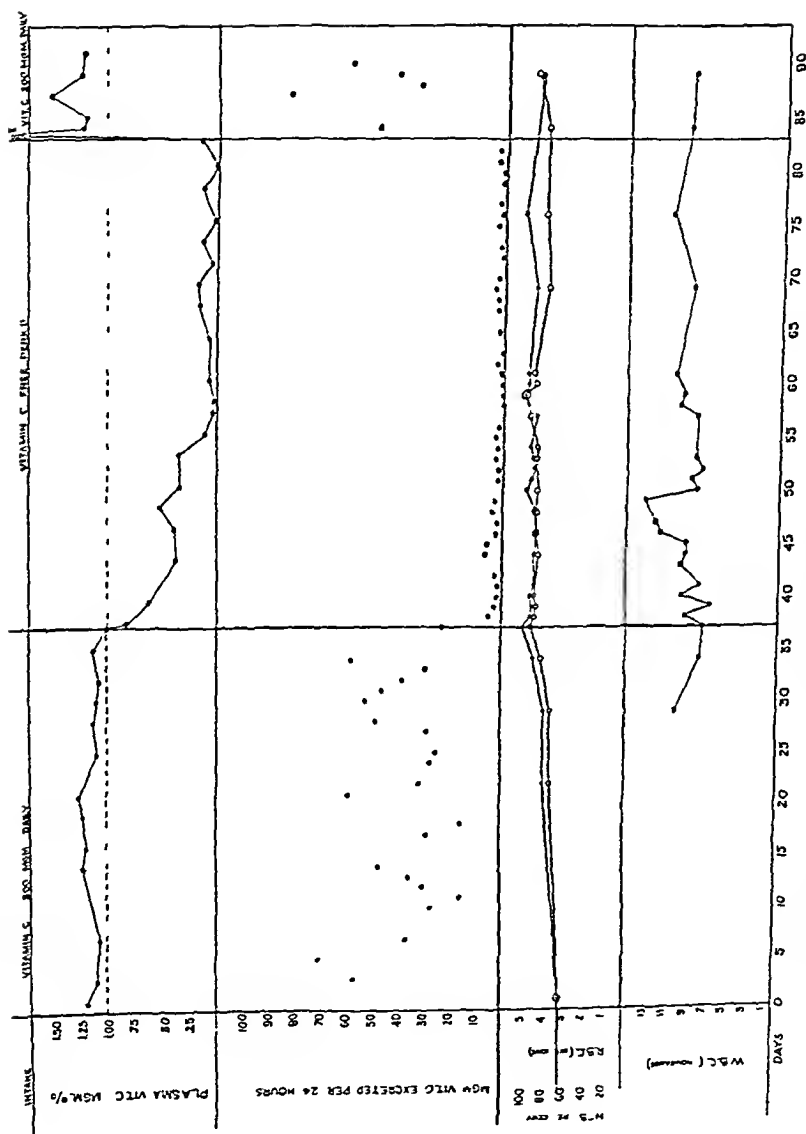
individual, that is, about 96 mg daily. Similarly, when his tissue stores were saturated, and more than 100 mg was fed daily, this patient behaved as a normal subject, and excreted the excess.

*Case #44* was a 62-year old Italian white male, admitted on March 27, 1939. He had been suffering from pain and limitation of motion of the right knee, of eight days' duration. He was an unemployed tailor who lived alone and cooked for himself. Because of the poor condition of his teeth, he ate soft foods. He had not had any citrus fruits or fresh vegetables for three months. About eight days prior to admission he noticed a purpuric patch on the right knee. There had been no trauma associated with this. The knee began to swell and became so painful that the patient was unable to bear any weight on it or move the knee joint without exquisite pain. Eventually the pain became so severe that the knee could not be flexed. The patient also complained of soreness and burning of the tongue for the past few months. On examination he appeared chronically ill and pale. He was not dyspneic nor cyanotic. The tongue was smooth and pale. The gums were reddened, spongy, and piled up about the few carious teeth that remained. The lungs were clear. The heart was not enlarged and the sounds were of fair quality. The blood pressure was 100/60. The liver was enlarged and firm and extended two fingers below the costal margin. The spleen was not palpable. There was edema of both lower extremities, the left greater than the right. The right knee was swollen and the thigh and knee were discolored, due to extravasation of blood into the subcutaneous tissues. This discoloration was also seen over the leg and upper surface of the foot. On the inner aspect of the right thigh above the knee joint, more extravasation of blood had occurred. The reflexes were normal. The vibratory sense was intact. There was bilateral calf muscle tenderness but no other neurological signs of peripheral neuritis.

*Laboratory data* The urine was negative. R B C 1.87 million, Hgb 35 percent (5 grams), color index, 1, hematocrit, 16 percent, mean corpuscular volume, 83, fragility of cells, normal, W.B.C. 7,600, polymorphonuclears 57 percent, lymphocytes, 29 percent, monocytes, 7 percent, eosinophiles, 3 percent. The Wassermann was negative. Platelets were numerous. Bleeding time was two minutes. Non-protein nitrogen was 34 mg percent, blood sugar, 138 mg percent. Icteric index, 12, Vandenberg direct delayed, indirect, positive. X-rays of the bones were normal. The left knee showed no gross pathological changes of the bony structure. Slight hypertrophic synovitis was present. There were no gross changes of the shoulder joints, elbow joints, wrist, knee, or ankle joints. The lungs were clear. There was accentuation of the left ventricular curve of the heart.

Because of the extensive subcutaneous hemorrhages and the history of dietary inadequacy, and the absence of any other evidences of blood dyscrasias, the diagnosis of scurvy was made. In view of the patient's condition, vitamin therapy was begun immediately. The patient was given 2000 mg of vitamin C intravenously daily for the first 2 days, and 1000 mg on the third day. He was then fed 500 mg of vitamin C daily for 13 days. The patient received a total of 12.8 grams of vitamin C in the period of intensive treatment. The hemorrhages resorbed and the anemia improved, so that by the end of the period the RBC was 3.17 million, and the hemoglobin was 64 percent. The further details on this case are shown in Chart 4. The patient was next given 200 mg of vitamin C daily in divided doses for 43 days. This kept the plasma level above 1.0 mg percent. The urinary excretion averaged 44.5 mg daily, so that the retention was about 155 mg daily. The blood count had by this time become normal and all the symptoms of scurvy had disappeared. At this point the administration of vitamin C was discontinued and the patient was continued on the control diet, which was devoid of vitamin C. This regime was continued for 45 days, and during this time, with absolutely no vitamin C in either the diet or the crystalline form, the red blood cell count remained normal, and there were no significant changes in the hemoglobin or white blood cells. The plasma concentration and the urinary excretion of the vitamin fell rapidly and by the 20th day the former was 0.11 mg percent and for the next 25 days it ranged between zero and 0.2 mg percent. The urinary excretion was 2 mg daily. After 15 days the gums bled on slight pressure and mild changes were observed. Petechiae were observed on the 18th day over the lower extremities but these were transient. The gum changes did not progress. The patient had no complaints and there were no signs about the knee joints such as had been present on admission. On the 45th day of this vitamin C-free period the patient was given 3,000 mg of vitamin C intravenously in doses of 1,000 mg each. Fifteen minutes after the last dose the plasma concentration of the vitamin was 7.05 mg percent, 808 mg of vitamin C was excreted in the next 24 hours, and by the next morning the plasma vitamin C had fallen to 1.04 mg percent. The patient was then fed 200 mg of vitamin C daily for 7 days. The plasma averaged 1.02 mg percent and the excretion of the vitamin was 53 mg daily, so that 147 mg was retained daily. This was greater than the amount that a normal subject would have retained.

This case again demonstrates the prolonged increased requirement for vitamin C in patients with scurvy. It further demonstrates that full-blown scurvy will not occur within a period of 45 days on a



CASE NO 44

vitamin C-free diet, even in a patient recently cured of the condition. The rapid fall in plasma vitamin C and in the urinary excretion that followed the omission of vitamin C from the diet did not signify a complete depletion of the body stores of the vitamin. Had the diet been continued long enough to absolutely deplete the body of all its vitamin C, the patient would probably have developed the same hemorrhagic symptoms which he had had on admission.

*Case #45* was a 72-year old male admitted June 20, 1939. His chief complaints were itching of the legs and a purpuric eruption over the skin, of three weeks' duration. He had a dislocation of the left shoulder in 1934, and on setting the arm the fingers had become paralyzed. The fingers were still in this condition on admission. His diet had been inadequate for several years and in the past few months he had eaten very little, due to loss of appetite. He had also had diarrhea for the past few months. Three weeks before admission he noticed swelling of both feet. For the past two weeks there had been a purpuric eruption over the fingers of the left hand and over both legs. This had gotten progressively worse. On examination the patient seemed fairly well nourished. The gums were filthy but not spongy and they did bleed easily. The lungs were clear. The heart was not enlarged and the sounds were of fair quality. There were no murmurs. The blood pressure was 110/80. The abdomen was negative. There was a two-plus pitting edema of the legs and ankles. The skin over both legs was scaly and there was a purpuric rash. There were scattered petechiae on the thighs. There was moderate calf muscle tenderness and solar hyperesthesia. The knee jerks were normal but the ankle jerks were absent. There was marked sclerosis of the peripheral vessels.

*Laboratory data* R.B.C.  $4.09$  million, Hgb 71 percent, W.B.C. 6,200, polymorphonuclears, 59 percent, lymphocytes, 29 percent, monocytes, 2 percent, eosinophiles, 1 percent. The urine showed an occasional red blood cell but was otherwise normal. The Wassermann was negative. Non-protein nitrogen was 31 mg percent, blood sugar, 80 mg percent, icteric index, 12, Vandenberg direct, delayed, indirect, positive. Albumin-globulin ratio was  $2\frac{4}{16}$ . The stools were negative for blood. X-ray of the gastrointestinal tract, including the gall bladder, was negative. The Rumpel-Leed test was positive. The plasma vitamin C was 0.05 mg percent. Because of the history of an inadequate diet, the clinical findings, and the very low plasma vitamin C, the diagnosis of scurvy was made.

The patient was placed on a vitamin C-free diet and received no ascorbic acid supplement for 12 days (Chart 5). The plasma vitamin C ranged between zero and 0.1 mg percent and the urine contained only small amounts of reducing substances. The patient's clinical condition remained unaltered and there was no improvement. On the 11th day he had a nose-bleed. On the morning of the 13th day vitamin C therapy was begun. 100 mg of crystalline ascorbic acid was injected intravenously. This procedure was repeated daily. Giving the vitamin C in this manner removed any doubt as to its absorption, and by using in a patient with scurvy the dose that a normal individual utilized optimally daily it was possible to compare the metabolism in the normal and scorbutic subject. Improvement in the clinical symptoms began on the third day of treatment and continued progressively in spite of the fact that the patient had several flare-ups of a chronic cholecystitis. After 23 days of 100 mg of vitamin C daily, the ecchymoses had practically disappeared. The gum changes improved. The urinary excretion of the vitamin never increased, however, and averaged the small amount of only 1.2 mg in 24 hours. The plasma concentration also remained low, averaging 0.13 mg percent. Thus after a total of 2,300 mg of vitamin C had been injected there was still no evidence, as reflected in the plasma vitamin C and in the daily excretion, of saturation of the tissues with the vitamin. In spite of this, marked clinical improvement had occurred. These observations agree with those of Butler and Cushman (21) who reported that when patients with scurvy were given ascorbic acid the vitamin was first stored in the white blood cell-platelet layer and the white blood cells were the first to become saturated. This preceded the rise in the plasma vitamin C, which apparently does not increase until other more important cells in the body have had their stores replenished.

*Case #46* was a 69-year old single, white, male iron worker who entered the hospital on September 7, 1939 because of inability to walk, of four weeks' duration. The family history was irrelevant. The past history included a traumatic fracture of the pelvis and ribs in 1909 and a chancre in 1898, for which he had had no treatment until 1926. At that time he was told he had "locomotor ataxia." He then received about 100 injections over a period of four years. He had also had gonorrhea in 1904. The patient had been a chronic alcoholic for years. The dietary history was not reliable. The present illness began two months prior to admission with weakness of his legs and knees. After four weeks, walking had become impossible. Four days prior to admission his ankles and feet had







begun to swell and he noticed numbness of the legs up to the knees. He had lost 40 pounds in the past year. His appetite had been poor for the past year. For several weeks before admission he had had diarrhea and difficulty in urination. On examination the patient appeared chronically ill. He was not dyspneic, orthopneic nor cyanotic. The pupils were equal, regular, and reacted sluggishly to light and accommodation. The teeth were in poor condition and there was slight piling up of the gums. The tongue was red and beefy, with smooth edges. The lungs were clear except for a few râles at the right base. The heart sounds were distant. There were no murmurs. The rate was 110 and the rhythm was regular. The area of liver dullness was extended well below the costal margin but the liver could not be palpated. The abdomen was distended. Bladder dullness extended half way up to the umbilicus. There was 2-plus edema of the ankles. Scattered ecchymotic spots were seen on the dorsum of the hands, of the right forearm, and on both upper arms. There were scattered petechiae on both legs and on the dorsum of both feet. The knee and ankle jerks were absent. The biceps and tendon reflexes were more active on the right than on the left. Pain sensation was absent over the left hand to just above the wrist. There was some hyperesthesia over the right hand. There was anesthesia over both feet up to the junction of the middle and lower third of the tibia. Vibratory sense was absent over both legs but position sense was intact. There was marked loss of strength of both lower extremities. Ankle drop was more marked on the left than on the right.

*Laboratory data* Urine examination was negative. R B C 3.4 million, Hgb 68 percent, spinal Wassermann negative, icteric index 15, Vandenberg direct, delayed, indirect, positive, spinal fluid chemistry, normal, non-protein nitrogen, 34 mg percent. X-ray showed a normal heart but there was a fusiform aneurysmal dilatation of the arch of the aorta. There was moderate demineralization of the bones of the feet. The electrocardiogram showed ventricular premature contractions. The plasma vitamin C was 0.24 mg percent. The Rumpel-Leed test was normal.

The ecchymoses and the low plasma vitamin C substantiated the diagnosis of scurvy. There were also evidences of vitamin B deficiency. As a test of the severity and of the degree of vitamin C deficiency the patient was placed on the vitamin C-free diet and for 52 days was given no additional vitamin C. The diet was adequate in every other respect and contained an ample amount of vitamin B (dried brewer's yeast). Owing to the urinary difficulties, 24-hour samples were not collected daily but several times weekly. The plasma concentration of vitamin C reached zero on

the 5th day of the diet and remained close to this during the next 47 days (Chart 6). The urines when done contained very small amounts of reducing substances. The ecchymoses which were present on admission appeared to improve somewhat at first with the rest of the clinical condition but on the 5th day gum changes began to appear. The gums were redder at the tooth margins and were piled up and bled easily. The next day new ecchymotic spots appeared over the forearms and there was a rash of petechiae over the left shin. A blood clot was noticed in the nose. As the period of observation continued many new ecchymoses appeared but at the same time the old ones faded rapidly. Showers of petechiae appeared and disappeared over the lower extremities. On the 18th day the patient complained of shooting pains in the knees. The gum changes continued mild although always definite as compared to the transitory quality of the hemorrhagic phenomena. In spite of the fact that the patient had to be catheterized frequently no bleeding occurred until the 22nd day. From then on bleeding accompanied catheterization rather readily. On the 31st day the patient complained of painful swelling of the ankles. X-ray did not show any pathology of the underlying bones. The edema persisted in spite of bed rest and complete digitalization. For the rest of the experimental period the findings remained about the same, that is definite but not marked gum changes, transitory ecchymoses and petechiae, edema of the ankles, and fleeting muscle and joint pains. No large hemorrhages occurred nor did any severe anemia develop. On the 53rd day the patient was given 4,000 mg. of crystalline vitamin C intravenously in divided doses. The peak in plasma concentration of the vitamin following the injections was 16.7 mg. per cent but by the next morning it had fallen to 1.66 mg. per cent. Of the 4,000 mg. injected, only 508 mg. of the vitamin was recovered in the urine. The patient had retained 3,442 mg. of vitamin C.

It seems from this study in which an individual with the signs of scurvy was kept for 52 days on a diet free of vitamin C that the amount of vitamin C that the body did retain after the massive dose represents approximately the amount stored in the human body. This figure corresponds with the figures calculated from the other cases. This patient, following the massive dose of vitamin C was given 100 mg. intravenously daily for 14 days with a view to finding out whether this dose would maintain a plasma concentration above 1.00 mg. per cent. Within 2 days the plasma level fell to 1.02 mg. per cent and on the 4th day it was 0.62 mg. per cent. From this it

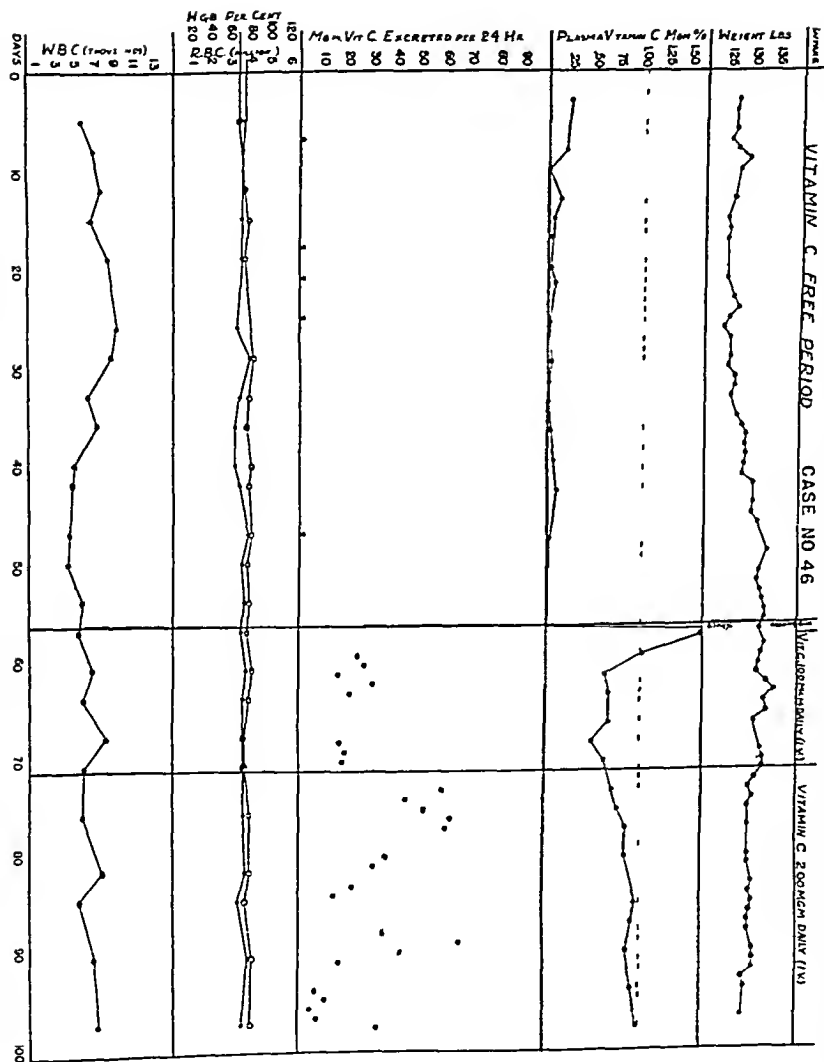


CHART 1. This patient, a 69-year-old male, was admitted with the clinical signs of scurvy consisting of ecchymoses and petechiae. The patient was kept on a vitamin C-free diet with no added vitamin C for a period of 47 days. There was no change in the hemoglobin or red blood cell count but the total white blood cell count fell slightly. The plasma level of vitamin C varied from zero to 0.1 mg per cent. Negligible amounts of vitamin C were excreted in the urine. On the 8th day of this diet the gums became redder and bled easily, and new ecchymotic spots appeared. On the 31st day the patient complained of painful swelling of the ankles. On the 53rd day 4,000 mg of vitamin C were given intravenously and the plasma level of vitamin C rose to 16.7 mg per cent. Following this the patient was kept on 100 mg of vitamin C given intravenously daily but in spite of the original massive dose the plasma level fell promptly, indicating that the patient's tissue stores of vitamin C were still not completely saturated. The amount of vitamin C given daily intravenously was raised to 200 mg after 26 days; the plasma level had reached 1 mg per cent, indicating that the patient's tissues were approximately saturated with vitamin C.

can be seen as in the other cases that once an individual has had scurvy it is not enough to saturate the tissues with one massive dose but to maintain them in this state it is necessary to provide the patient with a larger daily intake of vitamin C than is required in the normal subject. Apparently the amount required daily is about 200 mg of vitamin C which is twice as large as the amount necessary to maintain a state of saturation in normals.

In this case improvement in the clinical signs followed immediately upon the administration of vitamin C. The gum changes that had occurred in the latter period of the study regressed rapidly; the earlier changes more slowly. The old ecchymoses disappeared entirely as did the edema. This was particularly interesting as the edema had not responded to any other therapy such as digitalis, adequate protein and vitamin B. One will recall that 'swelling of the legs' was recorded in the earliest descriptions of scurvy. When it was found impossible to maintain the plasma concentration of vitamin C at a level above 1.00 mg per cent on an intake of 100 mg daily, the intake was increased to 200 mg daily, given intravenously in 100 mg doses. On this dose the plasma level rose slowly and on the 28th day was 1.0 mg per cent. The urinary excretion varied considerably, due probably to the fact that with intravenous therapy there was a short rapid increase in the plasma level. The average excretion was 3.4 mg daily. The patient was retaining about 16.4 mgm of vitamin C daily. By this time all physical findings attributable to vitamin C deficiency had disappeared. This case demonstrated several points also observed in the other cases: the chronicity of adult scurvy and the slow development of the pathological changes that are the basis of the physical signs. This patient had moderate signs of the condition when he was admitted to the hospital and when he was kept on a diet absolutely lacking in the vitamin for a period of 52 days the signs of scurvy increased very slowly and were not as extensive as those observed in some of the other cases on admission. The second point was that amounts of ascorbic acid ordinarily found optimal for normal adults, that is 100 mg daily, were incapable of maintaining saturation in a patient who had had the clinical signs of scurvy for a considerable period of time before the administration of a large amount of vitamin C. Case #45 showed that a daily dose

of 100 mg of vitamin C given intravenously will cure the signs of scurvy but will not effect saturation. All these cases bring out the fact that the amount of vitamin C necessary to cure the signs of scurvy is far less than the amount necessary to saturate the body.

In Table 7 we have summarized the urinary excretion, retention, and plasma levels of vitamin C in three normal individuals and in the five scorbutic patients just discussed. In the normal subjects the ingestion of 100 mg a day was accompanied by the maximum retention of vitamin C, approximately 90 mg daily, and on this dose there was a constant small urinary excretion of vitamin C, averaging from 8 to 13 mg daily (Charts 7, 8 and 9). Feeding more than this amount daily was apparently of no advantage in these normal adults, for when the amount of vitamin C ingested daily exceeded 100 mg, there was a prompt rise in the urinary excretion, and the excretion continued to parallel any increase in the amount ingested (Chart 10). Furthermore, on this daily intake of vitamin C it was possible both to raise and to maintain the plasma level of the vitamin at or slightly above 1.00 mg per cent. The fact that in the normal adult any intake of vitamin C over 100 mg daily was promptly excreted with no further significant rise in the plasma concentration indicated that this daily intake was capable of maintaining the tissues in a state of vitamin C saturation. In the scorbutic patients, on the other hand, the results show that 100 mg of the vitamin given daily, either by mouth or intravenously, could not raise the vitamin C level of the plasma. In one patient with scurvy (Case #45) after 23 days the plasma level was only raised from zero to 0.13 mg per cent, in another case (#42) 93 days of 100 mg daily only raised the plasma to 0.57 mg per cent. In another case in which the plasma vitamin C was raised to 1.66 mg per cent after a large dose, the daily administration of 100 mg was accompanied by a rapid fall in plasma concentration of vitamin C to 0.63 mg per cent. The maximum retention of vitamin C in the scorbutic patients was much greater than 90 mg daily, even for rather long periods of time following the beginning of vitamin C therapy, indicating the depleted state of the tissues. This is shown in Chart 11 in which are compared the daily urinary excretion and retention of vitamin C in the normal and scorbutic subjects on doses of 100 and 200 mg of vitamin C daily. This increased retention of

TABLE 7

Summary of the Excretion, Retention, and Plasma Levels of Vitamin C in 3 Normal and 5 Scorbatic Cases

CASE	PERIOD	NUMBER OF DAYS	DAILY INTAKE OF VITAMIN C	AVERAGE DAILY EXCRETION OF VITAMIN C	AVERAGE DAILY RETENTION OF VITAMIN C	PLASMA RANGE OF VITAMIN C
Normal cases						
L. R.	I	19	50	11 $\pm$ 4.6	39	0.97 $\rightarrow$ 0.80
	II	53	100	20 $\pm$ 5.3	80	0.80 $\rightarrow$ 1.12
	III	22	200	109 $\pm$ 20	91	$\leftarrow$ 1.14 $\rightarrow$
	IV	16	350	259 $\pm$ 48	91	1.25 $\rightarrow$ 1.41
W. J.	I	6	0	6.4 $\pm$ 3.9	0	0.30 $\rightarrow$ 0.20
	II	52	100	6.0 $\pm$ 4.4	94	0.20 $\rightarrow$ 1.07
Interval of 2 months						
A. T.	I	8	None	6.0 $\pm$ 2.0	0	0.56 $\rightarrow$ 0.27
	II	41	50	9.6 $\pm$ 5.2	40	$\leftarrow$ 0.28 $\rightarrow$
	III	43	75	7.9 $\pm$ 3.6	67	0.30 $\rightarrow$ 0.70
	IV	45	100	13 $\pm$ 3.7	87	0.70 $\rightarrow$ 1.20
	V	31	150	68 $\pm$ 14	82	1.20 $\rightarrow$ 1.50
	VI	30	50	13 $\pm$ 4.3	37	1.45 $\rightarrow$ 0.60
	I	12	None	None		1.70 $\rightarrow$ 0.35
	II	18	50	5.9 $\pm$ 2.3	44	$\leftarrow$ 0.30 $\rightarrow$
	III	25	75	6.2 $\pm$ 2.2	69	0.30 $\rightarrow$ 0.50
	IV	42	100	12 $\pm$ 3.3	88	0.50 $\rightarrow$ 1.20
	V	18	150	54 $\pm$ 14	96	1.15 $\rightarrow$ 1.25
	VI	19	50	7.0 $\pm$ 1.3	43	1.25 $\rightarrow$ 0.50
	VII	30	150	54 $\pm$ 15	96	0.50 $\rightarrow$ 1.25
	VIII	9	100	14 $\pm$ 2.9	86	$\leftarrow$ 1.05 $\rightarrow$
	IX	24	75	10 $\pm$ 3.2	65	1.10 $\rightarrow$ 0.80
Scorbatic cases						
42	I	9	None	0.0	0	0.00
	II	93	100	7.7 $\pm$ 6.5	92	0.00 $\rightarrow$ 0.57
	III	40	200	68 $\pm$ 12	132	$\leftarrow$ 0.70 $\rightarrow$
	IV	15	400	175 $\pm$ 17	225	$\leftarrow$ 0.73 $\rightarrow$
43	I	4	None	1.7	0	0.00
	II	1	4.000	1,668	2,332	0.15 $\rightarrow$ 12.9
						$\rightarrow$ 1.14
	III	52	200	49 $\pm$ 13	151	$\leftarrow$ 1.44 $\rightarrow$
	IV	32	150	49 $\pm$ 11	101	$\leftarrow$ 1.08 $\rightarrow$
	V	21	200	96 $\pm$ 25	104	$\leftarrow$ 1.16 $\rightarrow$
	VI	10	100	4.8 $\pm$ 1.8	95	$\leftarrow$ 1.18 $\rightarrow$

TABLE 7—*Concluded*

CASE	PERIOD	NUM- BER OF DAYS	DAILY INTAKE OF VITAMIN C	AVERAGE DAILY EXCRETION OF VITAMIN C	AVERAGE DAILY RE- TENTION OF VITAMIN C	PLASMA RANGE OF VITAMIN C
<i>Scurbutic cases—Continued</i>						
44	I	27	Total intake	12,800 mg		→1 22
	II	43	200	45 ± 19	155	←1 11→
	III	45	None	2 2 ± 1 5		1 0 → 0 11
	IV	1	3,000	1,113	1,187	0 18 → 7 05
	V	7	200	53 ± 19	147	→1 04 ←1 02→
45	I	11	None	3 3		0 04
	II	23	100(I V)	1 2 ± 0 6	99	0 00 → 0 13
46	I	52	None	1 0 ± 0 7		0 24 → 0 00
	II	1	4,000	508	3,442	0 00 → 16 7 →1 66
	III	14	100(I V)	19 ± 7 9	81	1 66 → 0 63
	IV	28	200(I V)	36 = 18	164	0 64 → 0 99

vitamin C in the scorbutic patients occurred even when the administration of the vitamin daily had been preceded by massive doses of the vitamin. Although rapid saturation of the tissues can be effected by such massive doses, maintenance of this state of saturation in the patient who has had the clinical signs of scurvy requires a continued daily administration of the vitamin in doses of about 200 mg daily.

In cases #44, #45, and #46, where capillary fragility tests were carried out throughout the studies by the Wright and the Dalldorf techniques, there was no observed correlation between the capillary fragility and the state of vitamin C nutrition of the patient. This test, it seems to us, may be positive in the patient with scurvy, but there are many factors affecting it, and as it is quite obviously not quantitative, its diagnostic value is limited. During the period of vitamin C-free diets no effect on the weight, red blood count, hemoglobin, white blood count, or differential count, was observed. It is probable that the adequacy of the diet in protein and iron was responsible for the lack of effect of the absence of vitamin C during the period of observation.

The treatment of the scorbutic patient, as far as the clinical signs of the disease are concerned, requires relatively small daily doses of



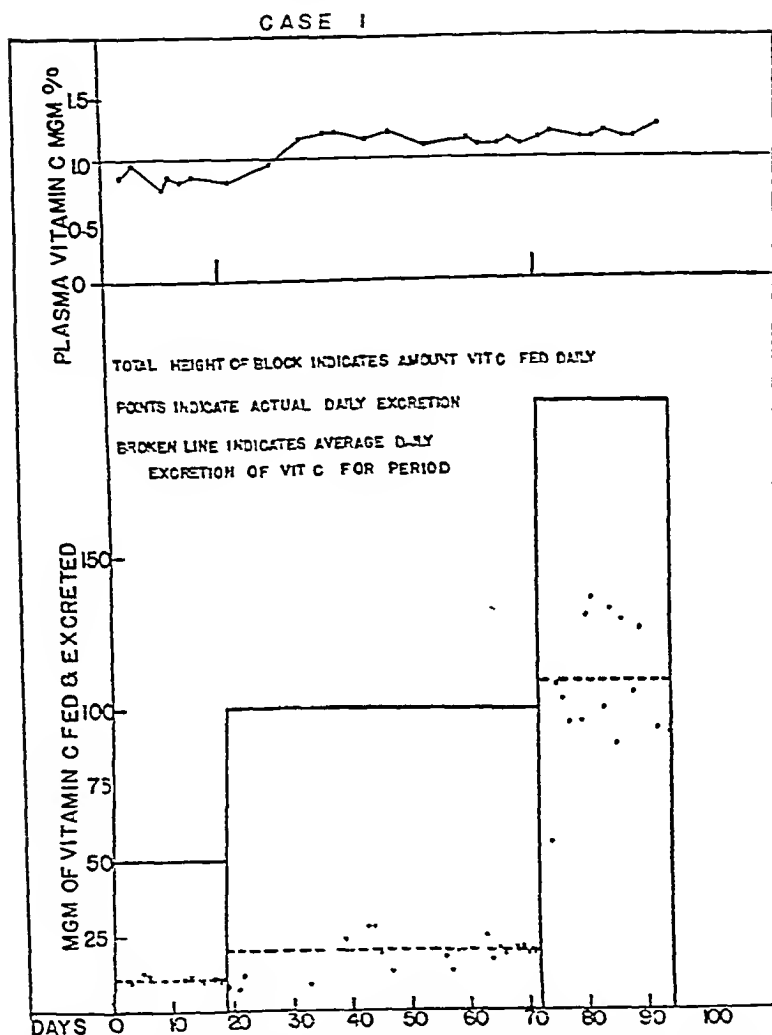


CHART 7 CASE 1 MGm. OF VITAMIN C FED AND EXCRETED DAILY AND PLASMA LEVELS OF VITAMIN C DURING EACH PERIOD

Reprinted from J. Clin. Invest., Vol. XVIII, 705-714, 1939 By Elaine P. Rall, Gerald J. Friedman and Sol Sherry

the vitamin. However, if the individual is to be returned to an optimal state of vitamin C nutrition, larger daily doses are required for fairly long periods of time.

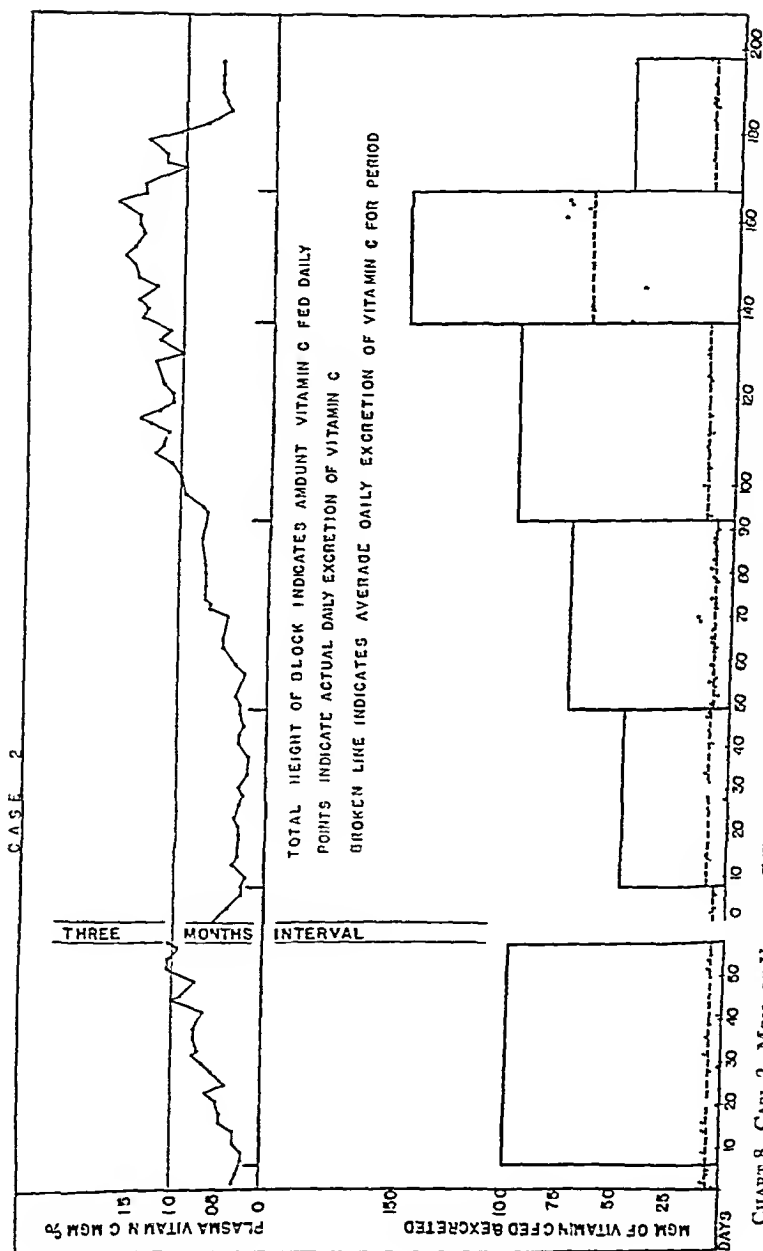


CHART 8 CASE 2 MG% OF VITAMIN C FED AND EXCRETED DAILY AND PLASMA LEVELS OF VITAMIN C DURING EACH PERIOD  
Reprinted from J Clin Invest, Vol XVIII, 705-714, 1939 By Elaine P Ralli, Gerald J Friedman and Sol Sherry

## THE ROLE OF VITAMIN C IN OTHER DISEASES

As mentioned previously, scurvy may accompany other pathological states or may be precipitated by such states. Although the state of vitamin C deficiency in other diseases may not be severe enough to produce the diagnostic symptoms and signs of scurvy, the level of vitamin C in the plasma may be low or zero. It would require a

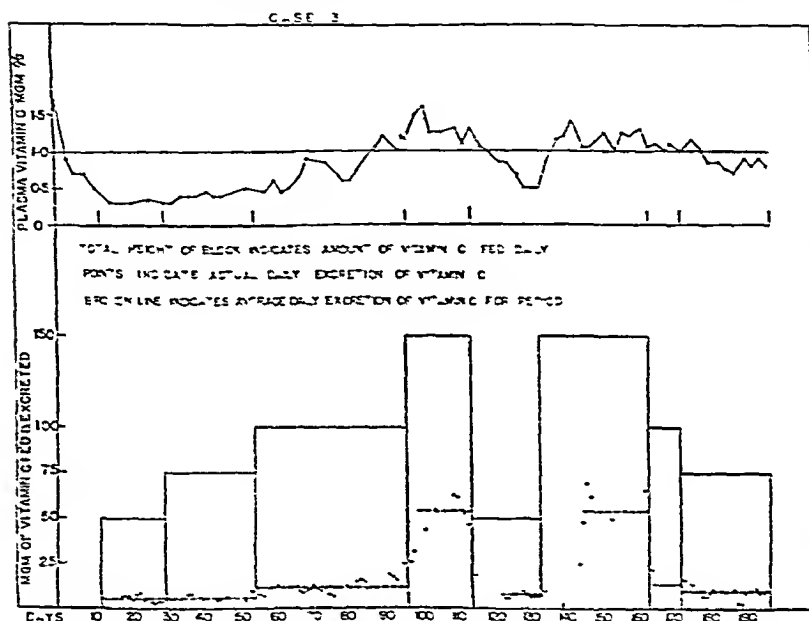


CHART 9 CASE 3 MG/M OF VITAMIN C FED AND EXCRETED DAILY AND PLASMA LEVELS OF VITAMIN C DURING EACH PERIOD

Reprinted from J. Clin. Invest., Vol. XVIII, 705-714, 1939 By Elaine P. Rall, Gerald J. Friedman and Sol Sherry

separate review to discuss all the diseases in which ascorbic acid has been used therapeutically. In many instances its use has been purely empirical and it has had no effect on the specific disease process or on the general condition of the patient. This discussion is confined to those conditions in which vitamin C has seemed to be involved either because clinical signs resembling those observed in scurvy were present or because the character of the lesion suggested that the daily requirement for vitamin C might be increased.

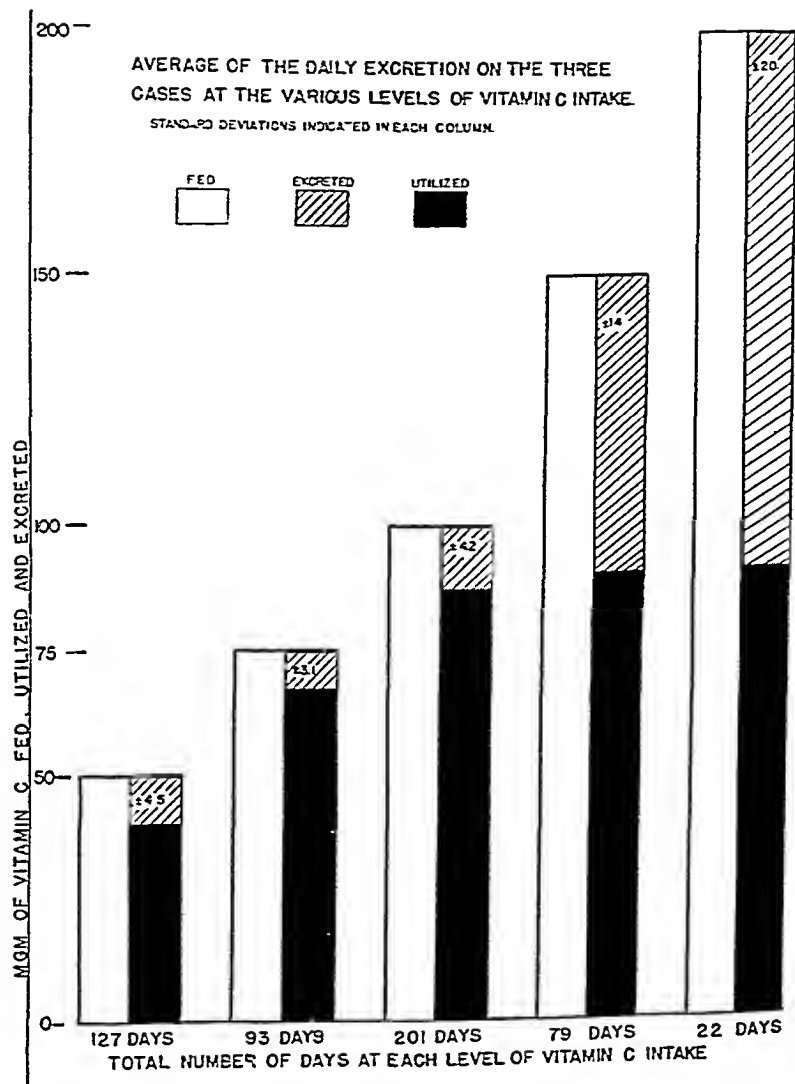


CHART 10 AVERAGE OF THE DAILY EXCRETION ON THE THREE CASES AT THE VARIOUS LEVELS OF VITAMIN C INTAKE

Reprinted from J Clin Invest., Vol. XVIII, 705-714, 1939 By Elaine P Ralli, Gerald J Friedman and Sol Sherry

*Diseases of the gastrointestinal tract* were among the first to be investigated as regards vitamin C both because the diet involved was low in the vitamin and because cases of scurvy had been reported in

patients treated for long periods with such diets (169, 39) Portnoy and Wilkinson (124) determined the level of ascorbic acid in the plasma and carried out saturation tests with vitamin C in 25 cases of

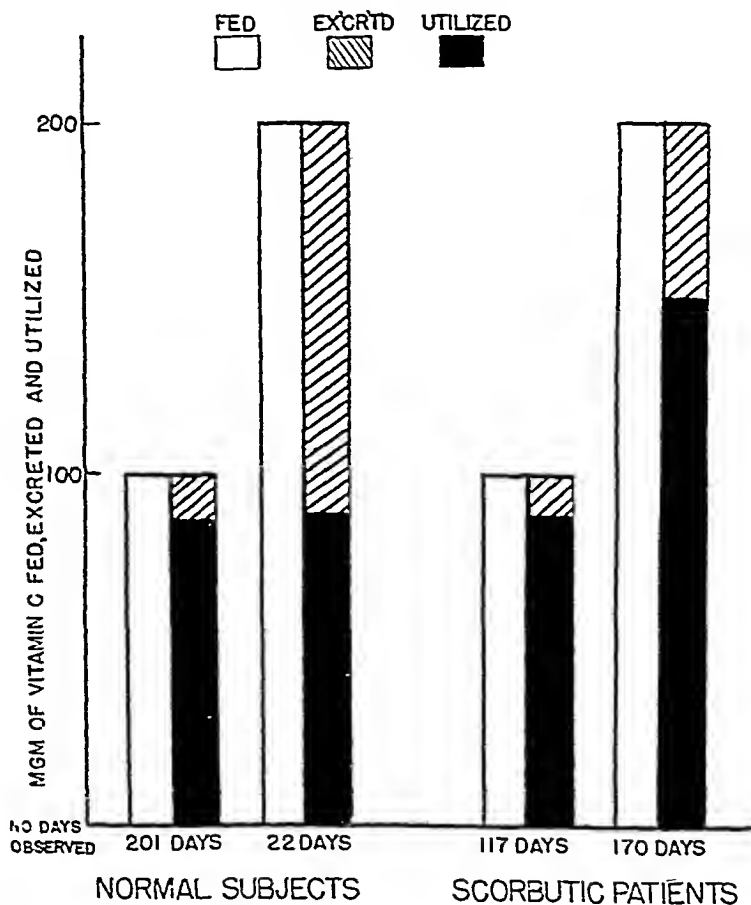


CHART 11 AVERAGE DAILY EXCRETION AND UTILIZATION OF VITAMIN C IN NORMAL AND SCORBUTIC SUBJECTS ON DAILY DOSES OF 100 AND 200 MG OF VITAMIN C

peptic ulcer without hematemesis and in 31 cases who had suffered from severe hematemesis. The determinations and tests indicated that the patients were suffering from vitamin C deficiency. The plasma ascorbic acid values ranged from 0.14 mg per cent to 0.59

mg per cent In this group of patients it was found that to saturate the tissues with vitamin C the patients with peptic ulceration required from 2,100 to 5,000 mg and the patients with hematemesis required from 2,000 to 8,000 mg Field and his associates (54) are emphatic in stating that the majority of patients with peptic ulcer have a deficiency in vitamin C They consider that the nature of the pathology of vitamin C deficiency is such that this deficiency may exert a deleterious effect on the healing of these ulcers Warren and his collaborators (169) drew attention to the negligible amounts of vitamin C in Sippy diets The first week Sippy diet contains only about 5 mg and the fourth week diet, about 15 mg of vitamin C They studied the amounts of ascorbic acid required to saturate 5 patients with active duodenal ulcers and as a result of their observations advised giving 200 mg of vitamin C along with the ulcer diet We have seen at least two cases of severe clinical scurvy in patients who had been on Sippy diets for fairly long periods, and Davidson (39) reported three cases of scurvy on ulcer diets In patients suffering from sprue, ulcerative colitis, and paratyphoid enteritis, Lund and Elmby (103) found that ascorbic acid was poorly absorbed

These are only a few of the observations that have been made on the state of vitamin C nutrition in patients with gastrointestinal disease The evidence suggests that, owing to the type of diets used in the treatment of such disorders, and the interference in the absorption of foods, there exists a deficiency of vitamin C During the active phase of such diseases intravenous use of ascorbic acid is a simple and effective way of combating the deficiency if present There is no evidence that ascorbic acid will control the bleeding that may accompany such conditions or will affect the rate of healing of peptic ulcers in man

*Relation of vitamin C to gums and teeth* As one of the well known evidences of scurvy is the change that occurs in the gums, the therapeutic use of ascorbic acid in diseases of the gums has received considerable attention Roff and Glazebrook (133) observed in a large group of young men in England who were in the Naval Training Corps, that the administration of vitamin C had no effect on the marginal gingivitis This responded to simple hygienic measures They did find, however, that the gingivo-stomatitis lesions were

always cured after the subjects were saturated with ascorbic acid. Following 14 days of treatment with ascorbic acid the gums lost their deep maroon color and the tissues became firmer. The average amount of vitamin C required per patient was 4,000 mg. Boyle (19) studied the effect of ascorbic acid deficiency on enamel formation in the teeth of guinea pigs. On deficient diets there was a retardation of the deposition of dentine in the incisor teeth. The enamel was deposited at about the normal rate and when areas of hypoplastic enamel were seen, they were associated with scorbutic hemorrhages into the overlying tissue. Boyle does not feel that dental caries in man is related to a deficiency of vitamin C.

It seems to us that in view of the variety of factors that may affect the appearance and condition of the gums, one should not conclude that every gum lesion is due to a deficiency of vitamin C. We have repeatedly seen 'spongy' gums in subjects with carious teeth in whom ascorbic acid was still present in adequate amounts in the plasma. The same is true of bleeding gums. The gum change that does seem to be due to a deficiency of vitamin C is the hemorrhagic lesion which is associated with an accumulation of blood in the gums. Many of the other gum changes are probably due to underlying dental pathology.

In experimentally induced *hyperthyroidism* in rats Sure and Theis (150) observed a decrease in the vitamin C concentration of the adrenals, thymus, thyroid, pituitary, kidney, liver and heart, from which it is concluded that the vitamin C content of the endocrines and tissues of the rat suffer tremendous losses of this vitamin following toxic doses of thyroxine. It is reasonable that with an increase in the rate of metabolism the utilization of vitamin C would be increased. The effect of hyperthyroidism in patients was studied by Lewis and others. Lewis (98) observed 5 patients before and after subtotal thyroidectomy. The vitamin C content of the diet was kept constant and the excretion of vitamin C in the urine was determined. In all the patients the vitamin C excretion before operation was less than normal. The actual daily excretion during the period of hyperthyroidism was from 4 to 10 mg. Following thyroidectomy the vitamin C excretion increased in all the patients. These observations were confirmed by Spellberg (155). We observed one case of scurvy

in a patient with hyperthyroidism. Clinical scurvy as a complication of hyperthyroidism is apparently infrequent.

The question of vitamin C deficiency as a possible etiological factor in *rheumatic fever* was suggested by Rinehart (132) as a result of studies on animals and later in human beings. His general conclusion was that rheumatic fever resulted from the combined effects of vitamin C deficiency and infection, and that vitamin C deficiency might be a factor in the etiology of some cases classified as rheumatoid arthritis. This point of view has been challenged by Schultz and by Taylor. Although Schultz (140) agrees that a non-purulent carditis occurs in guinea pigs with chronic scurvy which are infected with *Streptococcus hemolyticus*, he feels quite definitely that the lesions produced are not characteristic of those found in rheumatic fever. In this respect Taylor (161) agrees with Schultz. Furthermore Faulkner (53) considers that the low level of vitamin C in the plasma of patients with rheumatic fever is probably the result of the infection rather than its cause. The reports of Abbasy and his associates (2) and of Hall et al (66) that patients with rheumatoid arthritis require more vitamin C than normal subjects cannot, it seems to us, be interpreted as meaning that such an increase in requirement is specific for this particular disease. The same statement as regards vitamin C requirement has been made for a variety of other diseases such as pneumonia, tuberculosis etc. Recently Kuttner (95) reported that the addition of vitamin C as well as some of the other vitamins did not reduce the incidence of recurrences of rheumatic manifestations in children with rheumatic fever.

The confusing reports on the amounts of vitamin C required in various diseased states is probably due to the different methods used for estimating the vitamin C requirement and the lack of a uniform approach to such studies. It is most important that the dietary intake of the vitamin should be kept standard as the excretion of vitamin C in entirely normal subjects will be low until the vitamin C intake is above 100 mg daily. The observations reported thus far do not warrant inferring that vitamin C plays any part in the etiology of rheumatic fever or rheumatoid arthritis.

Various observers have reported a low plasma level of vitamin C and a diminished urinary excretion in a number of infectious diseases



such as diphtheria pneumonia typhoid, tuberculosis and osteomyelitis. When case 42 in our series developed an infection while on a controlled amount of vitamin C daily there was a fall in the plasma level and urinary excretion of the vitamin. It is quite likely that any general infection or any increase in the rate of metabolism might tend to increase the vitamin C requirement. As mentioned before the onset of an infection may precipitate the clinical signs of scurvy in patients who have been on a vitamin C deficient diet for long periods. However although the requirements for vitamin C may be increased as a result of infection, there is as yet no evidence that deficiency of the vitamin plays a specific role in susceptibility to infections.

The importance of vitamin C in the formation of the intercellular material led to investigation of its effect in *wound healing*. It was shown experimentally in guinea pigs (96) that abdominal wounds in scorbutic animals were not capable of withstanding as much pressure as those in normal animals. Gastric wounds of scorbutic pigs ruptured at the site of the wound and histologically these experimental animals showed connective tissue repair in the form of fibroblastic tissue but little collagen production. Wolfer and Hoebel (175) in discussing the significance of ascorbic acid deficiency in surgical patients report severe vitamin C deficiency in patients whose wounds failed to heal. This complication occurred particularly in patients with gastrointestinal diseases who had been treated with restricted diets. Preoperative saturation of such patients with vitamin C resulted in satisfactory wound healing. In this connection it is interesting to recall that Lord Anson (76) noted the reopening of old wounds in sailors on the long sea trips when scurvy was common.

The simplest way of discussing the effects of vitamin C deficiency on the production of *anemia* is to consider its effects in the different groups in which it has been studied namely the scorbutic guinea pig, infants with scurvy and adults with scurvy. In the guinea pig during the development of scurvy Sigal (152) observed a decrease in hemoglobin and in the number of red blood cells. An adequate intake of iron did not prevent the development of the anemia. Aron (8) points out that in studying the anemia in scorbutic guinea pigs older animals should be used, e.g. 4 month old pigs as young pigs are apt to suc-

cumb to the deficiency before the anemia manifests itself. He found a distinct reduction in the hemoglobin content and number of red blood cells in the older pigs on a scorbutic diet. The age of the pigs used may account for the irregularity in the occurrence of anemia in the scorbutic guinea pigs observed by von Euler and Malmberg (47). Hess noted (76) that in infants with scurvy anemia was not a constant finding and several other observers have supported this observation (4, 7, 134) and have also pointed out that if anemia does occur it does not parallel the severity of the symptoms of scurvy.

There has seemed to be a slightly greater tendency for anemia to be present in cases of adult scurvy, but in noting this fact one should remember that the diets in these cases are usually deficient in other respects. One cannot help questioning whether the absence of vitamin C alone from the diet can be considered responsible for the anemia that is observed. To support this statement there is the case of experimental scurvy produced in man (33), in which no appreciable anemia occurred in spite of a blood loss of over 6000 cc during the 6-month period of the deficient diet. A reticulocyte response in the anemia of several adult subjects with scurvy (107) and in a child with scurvy (117) has been reported. In both reports the effect of the protein intake was not evaluated. Of the 5 cases of scurvy which we observed, 3 (#43, #44, #46) had low red blood cell counts and a lowered hemoglobin. However, after treatment with vitamin C, case #44 was again placed on a diet deficient in vitamin C but adequate in every other respect. The anemia did not reappear, although no vitamin C was fed for 45 days. Similarly, in case #46, in whom the hemoglobin was 68 per cent and the red blood cells 3.4 million on admission, and who was kept on a diet devoid of vitamin C but adequate in every other respect for 52 days, and in whom the symptoms of scurvy were present, no further reduction in either the number of red blood cells or in the percentage of hemoglobin occurred. In view of the more recent observations on adult human scurvy, it does not seem that the absence of vitamin C can be considered solely responsible for the anemia that may be present. Apparently the same is true in the scorbutic infant. In the scorbutic guinea pig it is possible that vitamin C is more directly related to the anemia that has been observed.

*Vitamin C in relation to the white blood cells* In 1936 Stephens and Hawley (156) reported that the concentration of vitamin C was higher in the white blood cells than in any of the other fractions of the blood. This observation was confirmed by Butler and Cushman (21). This increased concentration of vitamin C in the white blood cells is of interest because of the many clinical conditions in which the white blood cells are involved.

Normally the concentration of vitamin C in the white cells varies from 25 to 38 mg per 100 grams of white cells. Butler and Cushman

TABLE 8

*Acute Experiment Demonstrating the Diffusion of Vitamin C, Intravenously Administered, from the Plasma to the White Blood Cells*

CASE	SPECIMEN	PLASMA CONCENTRA- TION VITAMIN C	MG VITAMIN C PER 100 GM WHITE BLOOD CELLS	PER CENT WATER IN CELLS	MG VITAMIN C PER 100 GM WET BLOOD CELLS	WHITE BLOOD CELL COUNT
No. 48, M. H. Chronic myelogenous leukemia	6-15-39 fasting	0.27	48.1	76.7	213	410,000
	20 minutes after injection 700 mg vitamin C	1.99	65.3	78.0	297	450,000
	60 minutes after injection 700 mg vitamin C	1.17	75.2	75.6	300	450,000
	6-19-39, fasting	0.28	51.7	74.4	200	525,000
	20 minutes after injection 1,000 mg vitamin C	4.57	92.8	76.9	402	530,000
	60 minutes after injection 1,000 mg vitamin C	2.02	81.7	77.9	370	615,000

(21) have reported concentrations as high as 100 mg per 100 grams of white cells in patients with leukemia. We have studied the ascorbic acid content of the white cells and the effects of the intravenous injection of vitamin C on the concentration of vitamin C in the white cells in three cases of leukemia. In case #48 a patient with chronic myelogenous leukemia (Table 8) the plasma vitamin C was 0.27 mg per cent and the vitamin C level of the white cells was 48 mg per 100 grams of white cells. The white blood cell count was 410,000. Ascorbic acid was given intravenously on two separate occasions (700 and 1000 mg). There was a rise in both the plasma and white

blood cell levels of vitamin C within 20 minutes. At the end of an hour the plasma level had fallen sharply but the white cell level of vitamin C remained elevated. This demonstrates a rapid diffusion of vitamin C from the plasma to the white cells, which is in marked contrast to the slow diffusion of vitamin C which occurs from the plasma to the red cells (74, 21). In both cases of chronic leukemia studied the concentration of vitamin C in the white blood cells was above the normal level. However in case #49, a patient with acute leukemia, the level of vitamin C in the white cells remained within normal limits even after the administration of massive doses of vitamin C (Table 9).

TABLE 9

*Acute Experiment on the Effect of Vitamin C on the Total and Differential White Blood Cell Count, in a Case of Agranulocytosis*

CASE	TIME	TOTAL WHITE BLOOD CELL COUNT	DIFFERENTIAL			
			Polymorpho-nuclears	Meta II	Lympho-cytes	Monocytes
No 47, M S Agranulocyto-sis	minutes					
	0	5,400	42	18	28	12
	Intravenous injection of 10 cc physiological saline					
	60	5,350	39	24	28	9
	Intravenous injection of 600 mg vitamin C in 10 cc physiological saline					
	15	4,500	34	20	36	10
	60	4,350	32	27	34	7

Our findings in the 2 cases of chronic leukemia are similar to those of Butler and Cushman (21). They do not mention whether any of their cases were of the acute type of leukemia. Obviously no final conclusions can be drawn from our single case, #49.

During the production of experimental scurvy in man, Crandon et al (33) observed a slight fall in the white cell count, which they did not consider significant. Following vitamin C therapy the white cell count rose. Other observers have reported a rise in the number of white blood cells following the administration of vitamin C. Muller (110) reported that in 9 of 12 subjects the injection of 100 mg of vitamin C resulted in an average increase in the white cell count of

13 per cent Schnetz (138) reported a slight rise in the white cell count following vitamin C therapy in a case of leukopenia. In a case of agranulocytosis which we studied, no effect on the number of white cells was observed following the intravenous injection of 600 mg of vitamin C (Table 10).

It is an interesting fact that the concentration of vitamin C in the white blood cells is greater than in the red blood cells or the plasma, but the significance of this finding in relation to the white blood cells has still to be investigated. Certainly as far as the leukemias are concerned there is no evidence that vitamin C will affect either the

TABLE 10

*Effect of Massive Doses of Vitamin C on the Plasma and White Blood Cell Concentration of the Vitamin in a Patient with Acute Leukemia*

CASE	DAYS	VITAMIN C INTAKE	PLASMA CON- CENTRATION VITAMIN C	A.S. VITAMIN C PER 100 GM WHITE BLOOD CELLS
		mg	mg per cent	
No 49, J S Acute leu- kemia	0	0	0.5	24
	20 minutes after injection, 3,000 mg vitamin C	3,000	21.3	26
	3	3,600	1.2	20
	7	5,200	1.0	27
	10	6,000	1.0	30

total number of white cells (10, 45) or that continuous vitamin C therapy will affect the course of the disease (35, 162).

*The Relation of Vitamin C to Addison's Disease* The fact that ascorbic acid is present in rather high concentrations in the adrenal glands (0.6 to 0.2 mg per gram) suggests a possible relationship between vitamin C and Addison's disease. There are, however, other tissues in the body that have as high a concentration of vitamin C as the adrenals (pituitary, corpus luteum). Several workers (172, 30, 77, 4, 153) have suggested that there is a relationship between the degree of pigmentation in patients with Addison's disease and the state of vitamin C nutrition. In fact Abt and Farmer (4) report the case of a negro in whom a dose of 400 mg of vitamin C daily over a period of several months produced 'a noticeable mottling depigmentation below the eyes'. In 2 cases of Addison's disease that we have



and there were one or two small areas of pigmentation in the buccal mucous membranes and on the tongue. Examination of the chest posteriorly showed slight curvature of the spine and there were scattered râles heard throughout both chests. The heart sounds were of poor quality, the rhythm was regular, and the blood pressure was 72/52. The routine urine examination was negative. The red blood cell count was 5.2 million, the white cell count was normal. The blood sugar was 70 mg per cent. The plasma chlorides were 86 millieq per liter. The basal metabolic rate was plus 6 per cent. X-ray of the chest showed no active evidence of tuberculosis, but an isolated calcific deposit in the right apex. The plasma vitamin C was 0.04 mg per cent. The patient, on questioning was found to be on a diet almost devoid of the vitamin as due to 'sour' stomach, she had for about 10 months taken no fresh fruits and very little vegetables.

TABLE 11  
*Vitamin C Requirement of a Patient with Ascorbic Acid Deficiency*

CASE	PERIOD	NUMBER OF DAYS	DAILY INTAKE OF VITAMIN C	AVERAGE DAILY EXCRETION VITAMIN C	AVERAGE DAILY RETENTION VITAMIN C	PLASMA RANGE VITAMIN C
No. 52, M.	I	14	150	87 = 10	63	0.8—1.1
Mc. Ad-	II	6	100	41 = 8.7	59	←1.1→
elson's dis-	III	13	50	9.5 = 2.7	41	1.1—0.8
ease						

The patient was treated with salt, fluids, and cortin for the obvious chloride deficiency and responded promptly. She gained weight. The plasma chlorides rose to 103 millieq per liter and the blood pressure rose to 114/72. She was given 200 mg of vitamin C daily and the plasma vitamin C rose to 0.9 mg per cent. During the period of hospitalization the patient received a total of 5800 mg of vitamin C. There was *no change* in the intensity or degree of the pigmentation. She was discharged after eight weeks to the clinic where she was kept on salt, vitamin B, and vitamin C. She did not attend the clinic regularly and was readmitted to the hospital in October, 1939. The physical findings were much the same as on the first admission. At this time the vitamin C requirement studies were done. She was fed a diet devoid of the vitamin plus a given amount of the vitamin in crystalline form daily (Table 11). The 24-hour urinary excretion of the vitamin and the plasma levels, were determined.

The results show (Table 11) that when the patient was fed 150

mg of vitamin C, daily, there was an average retention of 63 mg and the plasma level rose to 1.1 mg per cent. When the intake was decreased to 100 mg daily, the retention of vitamin C was about the same (59 mg daily) and the plasma level remained above 1.0 mg per cent. When the vitamin C intake was reduced to 50 mg daily, the retention was 41 mg and the plasma level fell to 0.8 mg per cent. The maximum retention of vitamin C that could be effected in this case was about 60 mg daily. Although this is lower than the total amount retained by normal male subjects on similar doses, calculated on the basis of the retention per kg of body weight, it was about the same (1.4 mg per kg of body weight). This amount was capable of maintaining the plasma level of vitamin C at 1.0 mg per cent. The maximum retention occurred when the patient was receiving 100 mg of vitamin C daily. Reducing the vitamin C intake to 50 mg daily was accompanied by a fall in the plasma level. This patient with Addison's disease behaved as a normal subject would on a daily dose of 100 mg of vitamin C. That the amount of vitamin C retained was maximum on 100 mg of the vitamin daily was shown by the fact that when the daily intake of the vitamin was raised to 150 mg there was a corresponding increase of vitamin C excreted, so that the retention remained about the same. The patient died after about six weeks in the hospital and at post mortem examination both of the adrenal glands were found to be entirely replaced by caseous tuberculous tissue, which finding confirmed the clinical diagnosis of Addison's disease.

*Vitamin C nutrition in diseases of the bone* In both experimental and infantile scurvy, changes in the bones may occur. Microscopically there is found rarefaction of the existing cortex, cessation of bone growth and replacement of the normal junction by a zone of collagen over poor connective tissue in which fragments of densely calcified cartilage are found. Dalldorf (36) points out that "the process suggests that in the absence of vitamin C the osteoblasts, unable to form osteoid tissue, revert to their prototype and attempt to form a fibrous union between the diaphysis and epiphysis." These observations suggested to us that it might be interesting to study the vitamin C requirements in patients with Paget's disease of the bone. The same procedure was used as in studying the requirement for



vitamin C in normal and scorbutic subjects The case studied (No 53) was a 59-year old male in whom the diagnosis of Paget's disease was made by x-ray As is shown in Table 12, the patient, on a dose of 100 mg of vitamin C daily, retained an average of 54 mg daily On this dose the plasma level of vitamin C was above 1.04 mg per cent, and feeding more than this daily was not accompanied by any significant increase in the retention, the excess being excreted in the urine When the daily dose of vitamin C was reduced to 50 mg daily the excretion dropped to 29 mg and the plasma level fell to 0.79 mg per cent This case differed from the normal subjects in that he did not retain as much vitamin C on a given intake as did the normals Notwithstanding this fact, on 100 mg of vitamin C daily

TABLE 12  
*Vitamin C Requirement in a Patient with Paget's Disease of the Bones*

CASE	PERIOD	NUMBER OF DAYS	DAILY INTAKE OF VITAMIN C	AVERAGE DAILY EXCRETION VITAMIN C	AVERAGE DAILY RETENTION, VITAMIN C	PLASMA RANGE, VITAMIN C
			mg	mg	mg	mg per cent
No 53, G Paget's disease	I	6	200	145 $\pm$ 16	55	0.88 $\rightarrow$ 1.04
	II	7	150	92 $\pm$ 7.1	58	$\leftarrow$ 1.04 $\rightarrow$
	III	6	100	46 $\pm$ 17	54	$\leftarrow$ 1.04 $\rightarrow$
	IV	8	50	21 $\pm$ 1.8	29	1.04 $\rightarrow$ 0.79

the plasma level of vitamin C was as high as in the normal subjects on this dose These studies do not show any clear cut change in the daily requirement for the vitamin in this case of Paget's disease Plasma vitamin C determinations were carried out in several other cases of Paget's disease and they paralleled the dietary intake of the vitamin

*Nephritis* Sendroy and Miller (148) and Wright (178) found that the low urinary excretion of ascorbic acid following the administration of the vitamin in patients with nephritis was due to the impaired renal function The plasma levels in the cases studied by Sendroy and Miller were all above 1.0 mg per cent, but in spite of this the urinary excretion was low In nephritis, they state that the "abnormally slow excretion of administered ascorbic acid does not necessarily indicate a low ascorbic acid content of the body"

*Vitamin C in alcoholism* Wortis and his associates (176) in a study of 103 patients with histories of chronic alcoholism found a normal level of vitamin C in the plasma and cerebrospinal fluid of subjects without psychoses or peripheral neuritis. In alcoholic subjects with evidences of peripheral neuritis and alcoholic psychopathy the vitamin C level was low in both the plasma and the cerebrospinal fluid. There is no evidence that the low ascorbic acid content in the plasma and spinal fluid was the factor primarily responsible for the psychopathic symptoms. They probably reflect a low dietary intake of the vitamin.

There are other conditions in which vitamin C has been used therapeutically but those discussed in this review are the ones in which the clinical findings had some basis for suggesting the use of the vitamin.

#### SUMMARY

The literature on ascorbic acid has been voluminous during the past five years, and in this review we have been unable to refer to all the studies which have contributed to the present knowledge of the subject. As one looks back at the reports of the 17th and 18th centuries it is significant that with scurvy, as with many other diseases, the earlier clinical descriptions of the disease have not been improved upon. The advances in our understanding of this condition have come through improved technical and chemical methods. The production of scurvy experimentally in guinea pigs laid the ground work for a more exact knowledge of the dietary factor involved. The microscopic picture of the lesion and the effects of feeding orange juice to scorbutic guinea pigs made it possible not only to postulate that this was a deficiency disease but it also provided objective proof that the lesion thus produced could be cured by this particular food.

The question then arose as to the existence of the prescorbutic states and of those degrees of vitamin C deficiency which were not profound enough to cause the clinical signs of scurvy, but on the other hand were not consistent with a state of normal vitamin C nutrition. Such prescorbutic, or vitamin C-deficient states, can only be diagnosed by the use of chemical methods, as the clinical signs of scurvy are not evident at such times. The question of which of the various methods should be used, and of how to define vitamin C deficiency and vitamin C subnutrition is one which still occasions considerable discussion and which seems to us to merit a few additional remarks.

Much of the confusion which surrounds the identification of the various states of vitamin C nutrition and the interpretation of the significance of the amounts of vitamin C excreted, is due to the fact that in the majority of the studies the vitamin C content of the diet has not been accurately controlled. Investigators have also overlooked the significance of the mechanism by which vitamin C is excreted and its dependence on the plasma concentration. It seems to us that the most satisfactory and simple method for identifying abnormal states of vitamin C nutrition is the determination of the level of vitamin C in the plasma and the white-cell-platelet layer. In subjects whose vitamin C nutrition is normal, the plasma level of vitamin C is above 0.7 mg per cent and the level of vitamin C in the white-cell-platelet layer is 25 to 38 mg per 100 grams of white cells. At the present time plasma levels of vitamin C below 0.7 mg per cent and down to 0.1 mg per cent are considered to indicate a state of vitamin C nutrition below the accepted normal. This is often referred to as a state of vitamin C subnutrition. When the plasma level of vitamin C is zero, the subject is considered to be deficient in vitamin C. If the deficiency of the vitamin is continued, the vitamin C content of the white-cell-platelet layer will decrease and eventually there will be no vitamin C in this fraction of the blood. The best index of vitamin C deficiency prior to the onset of the symptoms of scurvy, is the vitamin C content of the white-cell-platelet layer, as this is the last fraction of the blood to be depleted of its vitamin content and apparently reflects the content in the tissues. The difficulty that presents itself is the evaluation of the degrees of vitamin C deficiency on the basis of chemical determinations. The relation of these values to the physiological or pathological changes that may be taking place is not known at present. We do know that to maintain a plasma level of 0.7 mg per cent of vitamin C an individual requires about 75 mg daily, and that as the intake of the vitamin is lowered there is a corresponding decrease in the plasma level, which gradually falls to zero when the vitamin is entirely lacking in the diet. At just what point does this decrease of the vitamin in the plasma or white cells represent a deficiency of vitamin C? In human beings we have only one case report to go on, in which the chemical determinations of the levels of vitamin C in the blood fractions have been correlated with the onset of the symptoms of scurvy. In this case the symptoms of scurvy appeared

10 days after the level of vitamin C in the white-cell-platelet layer was zero and 90 days after the plasma level had reached zero. However, during the period of 90 days when the plasma level of vitamin C was zero, there was a steady fall in the level of vitamin C in the white cells. Obviously, then, once the plasma level of vitamin C has reached zero, the white cell layer will begin to fall. It therefore seems reasonable to suggest that when the plasma level of vitamin C is zero, the patient can justly be considered deficient in vitamin C, and when the level in the white cells has reached zero the deficiency is severe. Scurvy represents the most profound degree of vitamin C deficiency, and since it is preceded by a depletion of the vitamin C content of the plasma and cellular elements of the blood, the level of vitamin C in the plasma and the blood cells does serve as an index of vitamin C nutrition.

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# MARCH HEMOGLOBINURIA

## STUDIES OF THE CLINICAL CHARACTERISTICS, BLOOD METABOLISM AND MECHANISM\* WITH OBSERVATIONS ON THREE NEW CASES, AND REVIEW OF LITERATURE<sup>1</sup>

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<sup>1</sup> An abstract of the findings in the three cases of march hemoglobinuria reported here is included in the Proceedings of the Thirty-second Annual Meeting of the American Society for Clinical Investigation, May 6, 1940. *J. Clin. Investigation*, 19: 776, 1940.

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with a sterile syringe and needle rinsed with sterile saline several times. The blood was transferred to a tube containing a volume of three per cent sodium citrate solution equivalent to 10 per cent of the volume of the blood, and gently mixed. The sample was centrifuged immediately and the plasma separated with care to avoid any contamination with red cells. The hematocrit values were measured on a blood sample using oxalate mixture as anticoagulant. The plasma hemoglobin and bilirubin values obtained on the samples of citrated blood were corrected for dilution of the plasma due to the citrate solution. The plasma hemoglobin values obtained in normal individuals were usually less than five mgm per 100 c c and rarely as high as nine mgm per 100 c c when this technique of drawing the blood samples was used.

The plasma bilirubin concentration was measured by the method of Malloy and Evelyn (38). Any bilirubin values obtained in plasma samples with hemoglobin concentration of 30 mgm per cent or over have been discarded in accord with the finding in previous work (37) that the bilirubin values are lower than actual with this method in the presence of such concentrations of hemoglobin.

The urobilinogen contents of the stools and urines were measured according to the method of Watson (39).

The Donath-Landsteiner reaction was tested, with addition of guinea pig complement, as described by Mackenzie (40). The acid hemolysis test for hemoglobinuria of the paroxysmal nocturnal type was performed according to the method of Ham (41). The hemoglobin pigments of the blood and urine were identified by spectrophotometric studies employing a König-Martens type spectrophotometer<sup>3</sup>. Spectroscopic studies of the plasma and urine were made with a Zeiss hand spectroscope.

The urea clearance was measured by the method of Van Slyke, Page, Hiller and Kirk (42). The "urea plus ammonia" nitrogen was measured after urease action by the aeration method. The total protein of the urine was measured by the gravimetric method employing precipitation with acetic acid as described by Folin (43) or with trichloroacetic acid as in other studies in this laboratory (37).

<sup>3</sup> These spectrophotometric studies were made by Dr. John F. Taylor of the Department of Biochemistry, Harvard Medical School.

## INTRODUCTION

"March hemoglobinuria" is a condition in which physical exertion gives rise to the passage of a red urine containing hemoglobin in solution. The condition was first described by Fleischer (1) in 1881; 40 case reports are now available (1-31 incl.), mainly in the German literature. In 29 cases attacks of hemoglobinuria were precipitated by walking or marching for one quarter to several hours; in 11 cases, attacks occurred in athletes following strenuous runs. The published reports consist chiefly of a description of the clinical characteristics of the attacks. No study of the quantitative aspects of hemolysis is available, and information concerning the pathologic physiology of the syndrome is meager.

We have had the opportunity recently to study three cases of this condition. One patient, an insurance broker, developed hemoglobinuria on repeated occasions during short, brisk walks. The other two patients, college athletes, developed hemoglobinuria during strenuous runs of one and one-half and five miles.<sup>2</sup> The clinical and laboratory observations in these cases and a discussion of the literature are presented in this communication. The investigation included a study of the diagnostic criteria, hematological studies, chemical studies of blood pigment metabolism, studies of kidney and liver function, and physiological investigations of the conditions necessary for production of attacks.

## METHODS OF INVESTIGATION

Reticulocytes and platelets were counted in wet preparations according to the method of Damashek (32). oxalate mixture (33) was used as anticoagulant for measurement of the hematocrit values; the resistance of the red blood cells to hypotonic saline was measured according to the method of Daland and Worthley (34).

The concentrations of hemoglobin in the plasma and urine were measured by the benzidine method of Bing and Baker (35-36), with slight modifications as described in a previous paper from this laboratory (37). Blood samples were collected from an antecubital vein

<sup>2</sup> We are indebted to Dr. Michael E. Munson, Jr., of the Harvard University Hygiene Department and to Dr. Henry A. Kortell of the Urological Department, Beth Israel Hospital, for referring these patients to us for study.

in this kidney which was interpreted as possibly due to kinking of the ureter because of its lower position. The patient felt tired and was anxious about his condition at this time. Further urological examinations including cystoscopic examination and retrograde pyelographic studies revealed no abnormalities. The prostatic fluid was normal. During the course of the year prior to seeing us the patient had passed red urines on four or five occasions.

The patient consulted us because no diagnosis had been established. He stated that he believed that on each instance before passing the discolored urine, he had "perspired excessively, taken a long walk or eaten spicy food." The patient finally brought a fresh, dark red urine specimen to us and microscopic examination of the sediment of this specimen revealed no red cells. That the discoloration was not due to hematuria was thus finally established. Spectroscopic examination and positive benzidine and guaiac tests showed the presence of hemoglobinuria.

On repeated physical examinations during the next two years the spleen and liver were usually found palpable and there was a definite icteric tint to the sclerae and slight jaundice. Otherwise physical examination was completely negative. The posture was normal, and there were no orthopedic abnormalities in the opinion of an orthopedic consultant. There was no anemia, the electrocardiographic tracings were normal. Roentgen ray examination revealed enlargement of the spleen and liver.

During these two years of study only two "spontaneous" attacks of hemoglobinuria occurred. During the first of these two years, studies revealed that frank attacks were produced readily by brisk walks of one and one-half miles, during the second year the time and distance of brisk walking required to produce an attack gradually increased so that a 6.3 mile walk in an hour and a half failed to produce discoloration of the urine. The patient never noted a red urine after riding a bicycle for several miles or after a strenuous game of tennis. Detailed clinical and laboratory findings are reported in the text.

*Case 2* H. A., a college student, 19 years old, with a non-contributory family history and a history in childhood of pertussis, measles and mumps was referred to us for study because of repeated attacks of hemoglobinuria which had occurred two years previously following three or four mile runs during the college cross-country trials. The first one or two urines voided after these runs appeared deep red or brownish red following which the color was again normal. The advisory physician at the college found no red cells to account for the color of the urine and found the albumin and guaiac tests to be strongly positive. The patient usually had abdominal cramps,

The bromsulfalein excretion was measured according to the method of Rosenthal and White (44). The bilirubin excretion test was done according to the method of Weech (45), a solution containing 300 mgm of bilirubin was injected intravenously and the plasma bilirubin concentrations before and at appropriate intervals after the injection were measured by the method of Malloy and Evelyn (38).

The fragility of the red cells to trauma was tested essentially according to a method used by Aub et al (46). The red cells were washed three times with physiological saline and resuspended in saline to give 10 per cent by volume of red cells. The cells of a normal subject were similarly treated. Duplicate samples so prepared from both subjects were placed in test tubes of uniform size and all four tubes were rotated together for eight minutes. The samples were centrifuged immediately thereafter and the hemoglobin of the supernatant saline solution was measured by the benzidine method.

Measurements of oxygen consumption and of blood lactic acid in experiments in which work was performed on the treadmill and bicycle ergometer were made in the Fatigue Laboratory of Harvard University under the direction of Dr. D. B. Dill.

## OBSERVATIONS AND DISCUSSION

### CLINICAL CHARACTERISTICS OF MARCH HEMOGLOBINURIA

#### *Case Reports of Three New Cases*

*Case 1* H. F., a single man, 28 years old, an otherwise well insurance broker, with a non-contributory family history and a history in childhood of measles, whooping cough and chicken pox consulted us two years ago because he had passed red urine on infrequent occasions during the previous two years. On these occasions he had noted the red color in a single urine specimen, the next urine voided appearing normal. He experienced no symptoms at the time of appearance of the reddish urines or at any other time. Shortly after the first attack he consulted a urologist who found no abnormalities in the urine specimen collected at the time of examination, or in the urinary tract. A year later he still occasionally noted that his urine appeared red or reddish brown, he consulted two other physicians at this time, one a urologist. Again the urine specimens examined, and the urinary tract appeared normal except that roentgen ray studies showed the right kidney slightly lower than the left, and the presence of a slight shadow

His urine had always been normal at the time of several routine examinations during the year and a half previous to this attack. Six years ago he had a bloody urine, diagnosed as hematuria, for three days following a high dive with injury to his back.

Physical examination revealed nothing abnormal. There was no jaundice. The spleen and liver were not palpable. The posture was normal. There was no anemia, routine urine examinations revealed nothing abnormal, the electrocardiographic tracings were normal.

TABLE 1

*Clinical Data in the Three Cases of March Hemoglobinuria of This Study*

	CASE 1	CASE 2	CASE 3
Sex.	Male	Male	Male
Attacks precipitated by	Walking	Running	Running
Age at onset of attacks	26 yrs	17 yrs	19 yrs.
Time to date since first attack	4 yrs.	2 yrs	1 yr
Remission to date	Partial	0	0
Symptoms with attacks	0	+, 0	0
Significant past history	0	0	0
Family history of hemoglobinuria	0	0	0
Chronic icterus	+	+	0
Spleen palpable	+	0	0
Liver palpable	+	0	0
Anemia	0	0	0
Posture	Normal	Normal	Normal
Other physical findings	Normal	Normal	Normal

Three weeks after the first attack of hemoglobinuria the patient ran five miles in 31 minutes, the urine was straw colored after the run and contained albumin and no hemoglobin, the plasma was pigmented reddish with hemoglobin. A year later after a similar run in an intercollegiate track meet there was hemoglobinemia, albuminuria, and a trace of hemoglobin in the urine. Detailed laboratory studies are reported in the text.

#### *Resumé of Clinical Findings in Cases Reported Here*

The three cases of march hemoglobinuria reported here occurred in young men aged 17 to 26 years (Table 1). The family and past histories were not significant in respect to the attacks of hemoglobinuria. All of the patients had normal posture. The athletes showed albuminuria at no time except after strenuous runs, the

mostly in the right upper quadrant, at the end of those runs following which he passed a red urine specimen. Occasionally he had these cramps without passing a red urine, and occasionally he passed a red urine without abdominal cramps. The patient's urine examined on occasions before these attacks had not shown albumin or other abnormalities. The urine was found normal again on examination the day following these attacks. Because of the hemoglobinuria, the patient gave up competition in this sport. Since then he has run shorter distances, or even the same distance at a slower pace without developing hemoglobinuria. A red urine had never been noted after skiing, playing tennis, or the performance of any physical exertion other than fast runs.

The patient was a strong, muscular youth. Physical examination revealed nothing abnormal except an icteric tint to the sclerae. The spleen and liver were not palpable. Roentgen ray examination of the abdomen showed no enlargement of the spleen or liver, the right kidney appeared somewhat large, but normal in contour. The posture was normal. The electrocardiographic tracing was normal. There was no anemia, routine urine examinations revealed nothing abnormal.

On request the patient made three fast runs of one to three miles and passed a red urine on each occasion. In two instances he developed abdominal cramps, in the other instance he had no symptoms. Microscopic examination of the urinary sediment following these runs revealed only very rare red blood cells. The red pigment of the urines was identified with the hand spectroscope as chiefly oxyhemoglobin. The detailed laboratory findings are reported in the text.

*Case 3* K. R., a college student, 19 years old with a non-contributory family history and a history in childhood of measles, whooping cough, chicken pox, and mumps, was referred to us for study because of passing a red urine containing dissolved hemoglobin following a five and one-half mile run in try-outs for the college cross-country track team. He had no symptoms with the attack other than the fatigue usual after such strenuous exertion. He reported the abnormal appearance of the urine immediately to the physician in the hygiene department, and another urine specimen was collected. This specimen was light red, contained only rare red cells, a large amount of albumin and showed a positive guaiac reaction<sup>4</sup>. The urine was normal again the following day. Two weeks later the patient ran approximately the same distance again and passed a straw colored urine which contained albumin but no hemoglobin.

<sup>4</sup> These data were collected by Dr. Michael E. Murray, Jr.

His urine had always been normal at the time of several routine examinations during the year and a half previous to this attack. Six years ago he had a bloody urine, diagnosed as hematuria, for three days following a high dive with injury to his back.

Physical examination revealed nothing abnormal. There was no jaundice. The spleen and liver were not palpable. The posture was normal. There was no anemia. Routine urine examinations revealed nothing abnormal. The electrocardiographic tracings were normal.

TABLE 1  
*General Data on the Three Cases of March Hemoglobinuria of This Study*

	CASE 1	CASE 2	CASE 3
Sex	Male	Male	Male
Attacks precipitated by	Walking	Running	Running
Age at onset of attacks	26 yrs.	17 yrs.	19 yrs.
Time to date since first attack	4 yrs.	2 yrs.	1 yr.
Remission to date	Partial	0	0
Symptoms with attacks	0	—, 0	0
Significant past history	0	0	0
Family history of hemoglobinuria	0	0	0
Chronic atherosclerosis	—	—	0
Spleen palpable	—	0	0
Liver palpable	—	0	0
Anemia	0	0	0
Posture	Normal	Normal	Normal
Other physical findings	Normal	Normal	Normal

Three weeks after the first attack of hemoglobinuria the patient ran five miles in 51 minutes; the urine was straw colored after the run and contained albumin and no hemoglobin; the plasma was pigmented reddish with hemoglobin. A year later after a similar run in an intercollegiate track meet there was hemoglobinemia, albuminuria, and a trace of hemoglobin in the urine. Detailed laboratory studies are reported in the text.

#### *Resumé of Clinical Findings in Cases Reported Here*

The three cases of march hemoglobinuria reported here occurred in young men aged 17 to 26 years (Table 1). The family and past histories were not significant in respect to the attacks of hemoglobinuria. All of the patients had normal posture. The athletes showed albuminuria at no time except after strenuous runs; the

patient who developed hemoglobinuria on walking showed albuminuria only at the time of hemoglobinuria or after a walk sufficient to produce hemoglobinemia.

Two of these cases (Cases 1 and 2) had slight chronic icterus (Table 1) most evident in the sclerae. In the case in which hemoglobinuria developed on walking (Case 1) both the spleen and liver were at times palpable when no recent attack had occurred, enlargement of these organs was evident also on roentgen ray examination. On one occasion when the spleen was not palpable before exercise it became distinctly palpable at the end of exercise which produced hemoglobinuria. On several other occasions when the spleen was palpable before exercise it appeared more enlarged to palpation and percussion by two observers, after an attack. The liver, barely palpable on some occasions before exercise, was on one occasion felt as much as three fingers below the costal margin after an attack.

#### *Review of Literature with Comments*

All of the 40 cases of march hemoglobinuria reported in the literature are males.<sup>5</sup> The initial attack occurred between the ages of 16 years and 35 years. Several cases have been reported in which attacks occurred in soldiers on marching, for which reason the condition has been called "march hemoglobinuria."

There are 29 reported cases in which hemoglobinuria was precipitated by walking. Foerster (17) reported three cases, Gerhardt (15), Koelman (9) and Witts (27) each reported two cases and twenty other investigators each reported one case. Attacks occurred on walks of 15 minutes to three hours, usually one hour or more. Porges

<sup>5</sup> Jehle (47) in 1913 reported two cases of hemoglobinuria, one in a girl eight years of age and the other in a boy 11 years of age, which he diagnosed as march hemoglobinuria. A review of the histories and clinical findings in these instances indicates strongly that these patients more likely had paroxysmal hemoglobinuria from chilling (syphilitic type). Porges and Strisower (13) have also expressed this opinion. MacManus (48) in 1916 reported three cases of hemoglobinuria occurring in soldiers following "exposure to cold coupled with considerable bodily exertion." These cases were not diagnosed as cases of march hemoglobinuria by the author, however, they have been referred to as such by other authors. The description of the clinical characteristics of the attacks and the conditions under which attacks were precipitated indicate the diagnosis of paroxysmal hemoglobinuria from chilling in these instances also. None of these cases have been included in the following discussion of march hemoglobinuria.



and Strisower (12) demonstrated that in their patient hemoglobinuria occurred after 15 minutes of fast walking but did not occur after one hour of slow walking. Attacks in the reported cases usually occurred at intervals of weeks to months. Apparent recovery in most instances has occurred within a few months to two years. In a case reported by Koelman (9) apparent recovery occurred after 16 days during which five attacks were experienced on walks of 30 minutes or more, whereas a case reported by Witts (27) had periodic attacks during a seven year period and one of Foerster's (17) cases had attacks intermittently over a period of 20 years. It is interesting that no cases of march hemoglobinuria have been reported in women.

The duration of walks which produced attacks in Case 1 of our study and the frequency of attacks during his daily activity accord with the usual findings. For the past year and a half, beginning two and one-half years after the onset of attacks this patient has had no attacks during his daily activity, complete recovery might have been considered to have occurred except that our studies demonstrate that some intravascular hemolysis can still be produced by a fast walk of 6.3 miles, i.e., some four times the distance previously required for production of a frank attack. The amount of exercise which a patient who has had march hemoglobinuria must tolerate without occurrence of an attack in order to be considered recovered, has not been standardized.

In the cases reported in the literature, as in our cases, hemoglobinuria in a given attack usually is obvious for only one or two voidings. Foerster (17) and Finny (20) have reported exceptional cases in which attacks of hemoglobinuria lasted for three days following strenuous walks (17) or a strenuous run (20). Klein's (18) case had hemoglobinuria for 40 hours, Witts (27) described an attack of hemoglobinuria lasting for 18 hours after the patient ran up and down 1,000 six-inch steps in 15 minutes.

Apparently no desensitization occurs after attacks. For five attacks were produced in four days by walks of 30 to 40 minutes performed for the purpose of study in one of our patients (Case 1). Schellong (19) believed that the condition was improved in his case by a long period of bed rest. Kast (2) noted in his case that if several days elapsed between attacks a longer period of walking was necessary to produce

hemoglobinuria Complete bed rest for three days or the absence of attacks for six weeks did not alter the distance of brisk walking required to produce an attack in Case 1 of our series

Although only 11 cases have been reported in which hemoglobinuria resulted from strenuous runs (8, 11, 20, 28, 30, 31), certain published observations together with our own experience suggest that hemoglobinuria occurs more commonly following this exercise than is indicated by the small number of reported cases Dickinson (8), in 1894, reported two cases of hemoglobinuria in athletes, in one, attacks occurred after running three miles, in the other an attack occurred after a strenuous tennis match This author stated that it was recognized in English sport circles that the urine was sometimes red after a strenuous run during the beginning of training Attlee (28) reported two cases in boys 17 and 18 years of age who developed hemoglobinuria on running one or two miles Hantzschel (30) and Finny (20) each reported a case in which hemoglobinuria occurred after cross-country running or after running strenuously for a long time in a game of football (30) Fisher and Bernstein (31) have observed a case in which hemoglobinuria occurred after marathon runs Jundell and Fries (11), in 1911, in a study of the incidence of albuminuria during strenuous exercise observed four cases of hemoglobinuria in a total of 39 athletes running races of 10,000 meters (6.2 miles) or more That the incidence of hemoglobinuria after strenuous runs is greater than commonly believed is suggested by these statistics of Jundell and Fries (11) and by the fact that Dickinson (8), Attlee (28), and the present authors each have seen two patients with this manifestation of hemolysis following strenuous runs It is important that data which we present below demonstrate that hemoglobinuria, the only clinical manifestation of hemolysis following strenuous exercise, occurs only when the plasma hemoglobin is considerably increased To obtain further information concerning the incidence of intravascular hemolysis in strenuous exercise a statistical quantitative study of hemoglobinemia and hemoglobinuria following strenuous exercise is now in progress in this laboratory (49) In an unselected group of 21 Harvard cross-country runners we have found increased amounts of hemoglobin in the plasma of nine after runs of 2.6 to 5.1 miles In these nine the plasma hemoglobin concentrations following

the run ranged from 10 to 47 mgm per 100 c c and averaged 18 mgm per 100 c c (49), whereas the average value we have obtained in a large series of normal individuals is approximately 4 mgm per 100 c c with no cases with values higher than 9 mgm per 100 c c. Further recent studies in this laboratory (49) have also revealed three cases of frank hemoglobinuria in an unselected group of 22 marathon runners after a race of 26 miles and 385 yards, 18 of the 22 men showed plasma hemoglobin values above normal at the end of this race.

It is interesting in this connection that Feigl in 1916 (50) examined the plasma and urine of 27 subjects after an army pack march of 35 kilometers. Twelve of these subjects showed oxyhemoglobin in the plasma by spectroscopic analysis, several of these same subjects showed small amounts of hemoglobin in the urine by the benzidine test. This author made no mention of discoloration of the plasma or urine in these cases and quantitative hemoglobin measurements were not made (50). Foerster (17) in 1919 suggested that hemoglobinuria following strenuous marches might be physiological. An analogy is the occurrence of albuminuria (11, 51) and of decreased glomerular filtration (52) during strenuous exercises in subjects with normal kidney function and without albuminuria at rest or on moderate exercise. Hastings (53) has observed hemoglobinemia in untrained dogs after runs of 20 miles on the treadmill. Watson and Fischer (26) in 1935 suggested that march hemoglobinuria might be "an exaggeration, exemplified in certain predisposed individuals, of a more or less naturally occurring phenomenon."

There are usually no symptoms during attacks of march hemoglobinuria (1, 2, 3, 5, 6, 8, 9, 12, 14, 15, 23, 28) either during the exercise which gives rise to the hemolysis or during the subsequent period while hemoglobinuria persists. Chills have not been reported to occur. Fever has not been reported except in one very exceptional case in which collapse, unconsciousness for an hour, slight rise in temperature and hemoglobinuria for three days occurred in an untrained runner after a strenuous cross-country race (20). In some cases the patients have experienced abdominal pressure or pain of short duration during the attack (10, 26, 27), other patients have experienced a "sensation of heaviness" (4), or of "drawing" (18, 19), or weakness (31) in the lower back, or of pain in the lower back and

thighs (15, 17, 18, 31) Two of our cases had no symptoms at the time of the attack. In one case (Case 2) cramp-like pains in the abdomen sometimes occurred during a run resulting in hemoglobinuria, during some other runs when no hemoglobinuria resulted this patient also had these same symptoms.

Since symptoms are usually not experienced in patients with march hemoglobinuria during the exercise occasioning the hemolysis, the patient rarely associates the red urine, which may not be passed until hours later, with the exercise. This is particularly true in patients who develop attacks on walking, since the walk occasioning the attack may not be noticeably longer or brisker than frequently undertaken.

#### HEMATOLOGICAL OBSERVATIONS

None of the three cases of this study showed anemia or reticulocytosis (Table 2). There were no abnormalities of the red blood cells. The platelet and white blood cell counts were normal. The resistance of the red blood cells to hypotonic saline solution was repeatedly normal. Studies in two cases showed no decrease in blood hemoglobin or hematocrit during attacks of hemoglobinuria (Table 3). The white blood cell count and the resistance of the red cells to hypotonic saline were not affected by the attack in one case studied (Table 3). The fragility of the red cells to trauma (see Methods) in Case 1 was not greater than the fragility of a normal control. Autoagglutination of the red cells of Case 1 did not occur when the blood was incubated in the cold, at room temperature or at 37°C. Further, no hemolysis could be demonstrated in this case when cells of the same blood group (Group O) were suspended in the patient's plasma and the mixture similarly incubated.

The absence of anemia is a characteristic feature of this type of hemoglobinuria, only one case with slight anemia has been reported (14). Normal fragility of the red cells in hypotonic saline has been found repeatedly (12, 14, 17, 19, 27, 29). A very slight leukocytosis during attacks has been reported by some authors (14, 19), one of our cases (Table 3) and a case reported by Witts (27) showed no leukocytosis. In Witts' (27) case, as in our cases (Table 3), there was no change in red blood cell count, hematocrit, or blood hemoglobin during an attack. In the case reported by Fisher and Bernstein (31) the

red blood cell count and blood hemoglobin were found slightly lower than usual on a day following an attack of hemoglobinuria occasioned by a marathon run. Quantitative studies of blood pigment metab-

TABLE 2  
*Hematological Findings in the Three Cases of March Hemoglobinuria*

STUDY	CASE 1*	CASE 2	CASE 3
Red blood cells per cu. mm.	5,000,000	6,000,000	5,400,000
White blood cells per cu. mm.	10,000	8,200	10,500
Platelets per cu. mm.	555,000	603,000	
Blood hemoglobin, percentage	98	109	94
Hematocrit value, per cent cells	44	48	43
Reticulocytes per cent of red cells	0.3	0.1	0.1
Resistance of red cells to hypotonic salt solutions (trace of hemolysis, per cent salt)	0.48	0.44	0.44
Mean corpuscular volume (cu. micra)	88	80	80
Mean corpuscular hemoglobin (micro-micrograms)	31	28	27
Mean cell diameter (micra)			7.1
Blood group (International nomenclature)	O	B	A

\* In Case 1 the red count measured on six occasions during fifteen months ranged between 5,000,000 and 5,250,000, reticulocytes on five occasions were 0.0 to 0.8 per cent, platelet counts on three occasions were 517,000 to 749,000, the resistance of the red cells to hypotonic saline solutions on three occasions was normal.

TABLE 3  
*Hematological Studies following Attacks of Hemoglobinuria*

PATIENT	BLOOD HEMOGLOBIN		HEMATOCRIT		WHITE CELL COUNT		RESISTANCE TO HYPOTONIC SALINE SOLUTION—TRACE OF HEMOLYSIS	
	Before exercise, per cent	After exercise, per cent	Before exercise, per cent cells	After exercise, per cent cells	Before exercise, per cu. mm.	After exercise, per cu. mm.	Before exercise, per cent. sal. solution	After exercise, per cent. salt solution
Case 1			43.8	43.7				
Case 2	110	110	50.0	50.0	6,670	6,700	50	48

olism in the cases of our study as discussed below, demonstrate that the volume of red cells destroyed during an attack in these cases was so small that no anemia would be expected.

thighs (15, 17, 18, 31) Two of our cases had no symptoms at the time of the attack In one case (Case 2) cramp-like pains in the abdomen sometimes occurred during a run resulting in hemoglobinuria, during some other runs when no hemoglobinuria resulted this patient also had these same symptoms

Since symptoms are usually not experienced in patients with march hemoglobinuria during the exercise occasioning the hemolysis, the patient rarely associates the red urine, which may not be passed until hours later, with the exercise This is particularly true in patients who develop attacks on walking, since the walk occasioning the attack may not be noticeably longer or brisker than frequently undertaken

#### HEMATOLOGICAL OBSERVATIONS

None of the three cases of this study showed anemia or reticulocytosis (Table 2) There were no abnormalities of the red blood cells The platelet and white blood cell counts were normal The resistance of the red blood cells to hypotonic saline solution was repeatedly normal Studies in two cases showed no decrease in blood hemoglobin or hematocrit during attacks of hemoglobinuria (Table 3) The white blood cell count and the resistance of the red cells to hypotonic saline were not affected by the attack in one case studied (Table 3) The fragility of the red cells to trauma (see Methods) in Case 1 was not greater than the fragility of a normal control Autoagglutination of the red cells of Case 1 did not occur when the blood was incubated in the cold, at room temperature or at 37°C Further, no hemolysis could be demonstrated in this case when cells of the same blood group (Group O) were suspended in the patient's plasma and the mixture similarly incubated

The absence of anemia is a characteristic feature of this type of hemoglobinuria, only one case with slight anemia has been reported (14) Normal fragility of the red cells in hypotonic saline has been found repeatedly (12, 14, 17, 19, 27, 29) A very slight leukocytosis during attacks has been reported by some authors (14, 19), one of our cases (Table 3) and a case reported by Witts (27) showed no leukocytosis In Witts' (27) case as in our cases (Table 3), there was no change in red blood cell count, hematocrit, or blood hemoglobin during an attack In the case reported by Fisher and Bernstein (31) the

been demonstrated (57) that oxyhemoglobin in the urine of dogs changes on standing, either in the urinary bladder or in vitro to other hemoglobin products. Plugging of the tubules with hemoglobin pigments, hemoglobin casts and a brown sediment in the urine are observed after the intravenous injection of hemoglobin in rabbits and in dogs fed an acid diet (58-59, 60), whereas when these animals are fed an alkaline diet plugging of the tubules does not occur and the urine following such injections is bright red and clear, and contains only oxyhemoglobin. In vitro experiments have shown that methemoglobin and a brown precipitate, presumably acid hematin, are found after incubation of oxyhemoglobin in acid solutions of certain salt concentrations (58). We have observed changes in the color from red toward brown and precipitation of a brownish sediment in urines containing hemoglobin in march hemoglobinuria and other conditions when the urines have stood at room temperature for several days.

#### DIFFERENTIAL DIAGNOSIS OF THE PAROXYSMAL HEMOGLOBINURIAS

When a patient gives a history of passing a "pink," "red," or "black" urine the differential diagnosis between hematuria, hemoglobinuria, porphyrin (in which the urinary pigment is urofuchsin<sup>6</sup>), urinary pigmentation resulting from the ingestion of beets, or from the administration of phenolphthalein or of neoprontosil must be considered. A positive benzidine or guaiac test on a urinary specimen containing no red cells shows the presence of a free hemoglobin (or myoglobin) pigment. Since in urines of very low specific gravity or in urines which have stood for some time free hemoglobin may be derived from red cells, the final diagnosis of true hemoglobinuria is made by demonstrating free hemoglobin in the plasma during the attack.<sup>7</sup> The experience of one of our patients (Case 1) who consulted several physicians including two urologists and underwent intravenous and retrograde pyelographic studies in attempts to account for the history of

<sup>6</sup> Kark and Meiklejohn (61) have recently re-emphasized that the red color in the urine in porphyrin is not due to porphyrin, the pigment responsible for the color is urofuchsin.

<sup>7</sup> Rare cases of hemoglobinuria in the absence of hemoglobinemia have been reported in patients with acute nephritis (62), or infarction of the kidney (63), in the hemoglobinuria following infarction of the kidney, hemoglobin is present only in the urine from the infarcted kidney (63).

## NATURE OF HEMOGLOBIN PIGMENTS OF PLASMA AND URINE

Spectrophotometric examination of the plasma in two of our cases during attacks of march hemoglobinuria showed only oxyhemoglobin, with no methemalbumin or methemoglobin. In blackwater fever and in some other clinical conditions associated with hemoglobinemia, and especially those in which hemoglobinuria is prolonged, both methemalbumin and oxyhemoglobin bands have been observed in the plasma by spectrophotometric examination (54, 55). It is probable that methemalbumin would also be detectable in the plasma, at least by the Schumm test (56) in attacks of march hemoglobinuria in which the greater amounts of hemolysis occurred. In fact Lang and Braun (23) reported the presence of a faint band at 645–625  $m\mu$ , interpreted by them as due to the presence of hematin, in addition to oxyhemoglobin bands in the serum during an attack of march hemoglobinuria. In the light of Fairley's recent observations (56) that hematin does not exist free in human serum it is concluded that Lang and Braun's observations probably demonstrated the presence of methemalbumin in the serum of their patient.

The fresh urines voided during attacks were usually pink to dark burgundy red, and spectroscopic examinations showed mainly oxyhemoglobin, methemoglobin together with oxyhemoglobin was found by spectrophotometric examination of one acid urine four hours after it was voided (Case 1). In one instance a fresh acid urine contained a small amount of brownish sediment, presumably acid hematin (Case 1). We observed no hemosiderin or hemoglobin casts, and no, or only very rare, red cells in the urinary sediments.

In reported cases of march hemoglobinuria the urine during attacks has been variously described as pink to dark red and clear, or brownish red to dark brown with variable amounts of brown sediment. Oxyhemoglobin, methemoglobin, and hematin (10, 11, 15, 18, 23) and hemoglobin casts (1, 10, 11, 12, 17, 18, 19) have been found. Hemosiderinuria has been reported by only two investigators (2, 17). All investigators have found either no red cells or only very rare red cells in the urine during attacks.

The nature of the urinary pigments found in attacks of march hemoglobinuria probably depends chiefly on the acidity of the urine in the tubules and the freshness of the urine when examined. It has



urine specimen of Case 1, four hours after the urine was voided, revealed a point of maximum absorption at  $576\text{ m}\mu$  showing the presence of oxyhemoglobin and another at  $630\text{ m}\mu$  showing the presence of some methemoglobin (67). The finding of points of maximum absorption at  $576\text{ m}\mu$  in the plasma and urine of these cases establishes that the pigmentation was due to hemoglobin. The possibility that the pigment was oxymyoglobin was excluded since the point of maximum absorption of the alpha band of this pigment is  $581\text{ m}\mu$  (68).

TABLE 4

*Outline of Certain Diagnostic Criteria Utilized in Making Differential Diagnosis between the Various Types of So-called Paroxysmal Hemoglobinuria and the Findings in the Three Cases of This Study*

DIAGNOSIS	WASSER- MAN REACTION	DONATH- LAND- STEINER REACTION	ACID HEMOLYSIS TEST OF EAM	MYOGLO- BIN IN URINE OR PLASMA	HISTORY OF EXPOSURE TO FAVA BEANS	HEMOGLO- BINURIA PRECIP- ITATED BY WALKING OR RUNNING
Paroxysmal Hemoglobinuria from Chilling (Syphilitic Type)	—	+	—	—	—	—
Paroxysmal Nocturnal Hemo- globinuria	—	—	+	—	—	—
Myoglobinuria	—	—	—	+	—	—
Favism	—	—	—	—	—	—
March Hemoglobinuria	—	—	—	—	—	+
Results of Investigations in Cases of Present Study						
Case 1	—	—	—	—	—	+
Case 2	—	—	—	—	—	—
Case 3	—	—	—	—	—	+

In all three cases hemoglobinuria from chilling (syphilitic type) was excluded there was no history of syphilis, Hinton and Kahn tests were negative and the Donath-Landsteiner reaction was negative, in Case 1 immersion of the arm in ice water (Rosenbach test) for 30 minutes produced no hemoglobinemia or hemoglobinuria. The acid hemolysis test which is diagnostic of paroxysmal nocturnal hemoglobinuria (41) was negative in the cases of this study. There had been no history of ingestion of fava beans or exposure to the pollen of the fava plant (69, 70, 71). Finally attacks occurred in these cases

the occasional passage of red urine demonstrates the importance of early differentiation between hematuria and pigmentation due to dissolved hemoglobin or other dissolved pigments in patients complaining of passing a red urine.

There is no specific laboratory test for the diagnosis of march hemoglobinuria so that the final differential diagnosis must be made by ruling out the existence of the other types of paroxysmal hemoglobinuria and by demonstrating that attacks are produced by walking or running.

The German reviewers and more recently English (27) and American (64) authors refer to four types of so-called paroxysmal hemoglobinuria, namely, paroxysmal hemoglobinuria from chilling (syphilitic type), paroxysmal nocturnal hemoglobinuria, march hemoglobinuria, and paralytic hemoglobinuria (now known to be myoglobinuria). In these conditions attacks of hemoglobinuria are endogenous in origin and characteristically recurrent. Since favism may be confused under certain circumstances with these other types of recurrent hemoglobinuria, it will be included in the following discussion of differential diagnosis, in this condition an exogenous factor, namely, inhalation of the pollen of the fava plant or ingestion of the fava bean, causes attacks in sensitive individuals. The hemoglobinurias associated with acute infections, exposure to toxic chemicals, drugs, venoms, etc., need not be discussed here. French (65) and Mackenzie (66) have listed the many diseases and toxic agents giving rise to an attack of hemoglobinuria.

#### *Diagnostic Tests in Cases of This Report*

A resumé of certain criteria utilized in making the differential diagnosis between the various types of so-called paroxysmal hemoglobinuria and the results in the cases of this study are presented in Table 4.

Spectrophotometric studies were employed in two of the cases of this study to exclude the possibility that the urine and plasma pigments were myoglobin. Examination of plasma specimens of Cases 1 and 3 during attacks of hemoglobinuria revealed points of maximum absorption at  $576\text{ m}\mu$ . This band corresponds with that reported for the alpha band of human oxyhemoglobin (67). Examination of a red

nocturnal hemoglobinuria This abnormality is manifested in vitro by hemolysis on incubation of the washed red cells suspended in slightly acidified heparinized plasma or serum from the patient or from a normal individual with blood of the same group This acid hemolysis test is diagnostic of the condition The susceptibility of the red cells to hemolysis in the presence of increased acidity in this condition is manifested clinically by increased hemoglobinemia and hemoglobinuria during sleep or after the ingestion of acid forming salts (41)

In *paroxysmal hemoglobinuria from chilling* (syphilitic type) chills and fever vascular disturbances and frequently pain in the abdomen or back characterize the attacks (40) The paroxysmal attacks occur following exposure to cold The amount of blood destroyed during an attack is frequently sufficient to give rise to temporary jaundice and anemia The Wassermann reaction is almost always positive and a history of syphilis is usually elicited (40) In the serum of patients with the syphilitic type of hemoglobinuria there is a specific hemolysin which is activated by exposure of the patient to local or general cold This autohemolysin is detected in vitro by the Donath-Landsteiner test in which a mixture of the patient's serum or plasma with normal red cells of the same blood group is chilled and subsequently brought to body temperature in the incubator (78) hemolysis under these conditions demonstrates the presence of the autohemolysin The Rosenbach clinical test in which the patient's feet are immersed in ice cold water for about 10 minutes (78) results in production of an attack with typical symptoms with or without hemoglobinuria if the autohemolysin is present In the Ehrlich test a ligature is tied around the finger of a patient and this finger is immersed in ice water in the presence of the autohemolysin there is hemolysis in the blood drawn from the finger (40)

Recurrent hemoglobinuria is observed in *fascism* The hemolytic attack is occasioned in sensitive individuals by the inhalation of pollen from the plant '*Vicia faba*' or ingestion of fava beans The condition occurs chiefly in Sardinia Sicily and Southern Italy where the fava plant is grown in abundance and the bean is an important constituent of the diet (71) In attacks of rivism associated with hemoglobinuria, there are usually obvious anemia jaundice and other evi-

on walking or running and were reproducible when these exercises were repeated

### *Resumé of Diagnostic Criteria*

In addition to the laboratory tests outlined (Table 4), consideration of the clinical characteristics and other features of the various so-called paroxysmal hemoglobinurias is essential in determining the correct diagnosis

In paroxysmal attacks of *myoglobinuria* there are chills and fever and muscular weakness, stiffness and paralysis, and the urine is colored red by the dissolved muscle pigment, myoglobin (64, 68). The condition is frequently fatal. Myoglobinuria in man is extremely rare, excepting cases of *Haffkrankheit*,<sup>8</sup> we have found reports of but seven probable cases of myoglobinuria (64, 68, 73, 74), in only one of which was the urinary pigment identified spectrophotometrically (68). Myoglobin with molecular weight of 16,500 (68) is excreted by the kidneys with greater ease than hemoglobin with molecular weight of 68,000 (75) so that in cases of equine myoglobinuria the plasma is usually not at all or only very slightly discolored when the kidneys are excreting a dark red urine (76). This finding is to be contrasted with the finding of a definite discoloration of the plasma during the hemolytic attacks in all types of true paroxysmal hemoglobinuria. That the absorption bands of myoglobin and hemoglobin are different has been recognized only within the last few years.

In *chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria* (Marchiafava-Micheli disease) the hemoglobinuria occurs only, or is more severe, during sleep, so that the first morning urine is most deeply discolored. There is anemia, jaundice, a constant hemoglobinemia of varying degree, hemosiderinuria, and, frequently, reduced kidney function (41, 64). Ham (41, 77) has recently observed a fundamental abnormality of the red blood cells in paroxysmal

<sup>8</sup> Available knowledge indicates that the so-called "hemoglobinuria" of *Haffkrankheit*, a condition indigenous to the environs of Königsberg, Germany, which occurs after eating fish which contain a by-product of the cellulose factories there, may be myoglobinuria. Assmann et al. (72) have reported the finding of myoglobin by spectrophotometric examination in the urine of a patient and of a dog with this condition. Hamburger and Bernstein (64) have pointed out the similarity between the clinical and postmortem findings in *Haffkrankheit* and those in equine myoglobinuria.

The plasma hemoglobin concentration was highest at the end of exercise and gradually decreased to the normal level. The rate of fall was approximately the same as the rate of decrease of plasma hemoglobin following an intravenous injection of hemoglobin solution in normal individuals (Fig 1) (37-79).

In two of the patients (Cases 2 and 3) the plasma hemoglobin was always normal being approximately 5 mgm per 100 c.c. or less except after running. In Case 1 the plasma hemoglobin was normal on most occasions when no brisk walk had been undertaken (Table 5), on several other similar occasions, however the plasma hemoglobin was found to be 10 to 20 mgm per 100 c.c. In one instance in which the plasma of a control blood sample taken before exercise appeared very slightly hemolyzed another sample of blood was drawn before the exercise and 20 minutes after this first one. The second sample of blood likewise showed slight hemolysis and quantitative measurements showed the hemoglobin of the two samples to be 13 and 11 mgm per 100 c.c. respectively which findings indicate that this slight hemoglobinemia was actually present in the circulating blood and did not result from hemolysis due to any faulty technique in obtaining the plasma samples.

### *Hemoglobinuria*

Hemoglobin was excreted in the urine for one to three hours in the attacks of hemoglobinuria completely studied (Table 5, Figs 1 and 2, Case Reports). In Case 1 the total urinary hemoglobin excretion varied from 3 mgm to 458 mgm in the five attacks in which the total excretion was measured (Table 5), the amount excreted was roughly proportional to the height to which the plasma hemoglobin increased (Table 5). In Case 2 the total urinary excretion of hemoglobin after a one and one-half mile run was 22 mgm (Fig 1). On another occasion when this patient ran two miles a single urine specimen voided one-half hour after the run contained 90 mgm of hemoglobin per 100 c.c. In Case 3 there was no hemoglobinuria on one occasion of study after a five mile run which produced a hemoglobinemia of 27 mgm per 100 c.c. 2 mgm of hemoglobin were excreted in the urine after another five mile run which produced a hemoglobinemia of 24 mgm per 100 c.c. and considerable albuminuria (see below).

dences of marked blood destruction, chills and fever are usually present, and the hemoglobinuria lasts from one to three days (69, 70, 71)

The clinical features and laboratory findings in *march hemoglobinuria* have been discussed above and therefore will not be repeated in this place

The characteristics of these various conditions leading to recurrent attacks of hemoglobinuria differ markedly from each other in many respects, so that differential diagnosis can easily be made by appropriate laboratory and clinical studies

#### QUANTITATIVE STUDIES OF BLOOD PIGMENT METABOLISM

Quantitative studies of the blood pigment metabolism in attacks of march hemoglobinuria have not been reported in the literature. Measurements of the extent and duration of hemoglobinemia and bilirubinemia and of hemoglobinuria in attacks in the cases of the present study afford information concerning the nature of the attacks and the amount of blood destruction. The extent of blood destruction during attacks has also been estimated from studies of the fecal urobilinogen excretion

#### *Hemoglobinemia*

Hemoglobinemia was always present at the time of hemoglobinuria (Figs 1 and 2, Table 5). At the end of exercise sufficient to produce a pinkish to dark red urine in Case 1 the plasma hemoglobin varied from 35 to 210 mgm per 100 c c, the degree of hemoglobinemia during the eight month period from April to December, 1939, was roughly proportional to the distance walked at a given rate, later, progressively longer walks were required to produce any hemolysis (Table 5). The plasma hemoglobin in Case 2 was 75 mgm per 100 c c at the end of a nine minute run during which hemoglobinuria developed (Fig 1). In Case 3 the plasma hemoglobin was 27 mgm per 100 c c at the end of a five mile run in 31 minutes, there was a very slight trace of albumin in the urine at this time but no hemoglobin (Fig 1). A year later the plasma hemoglobin was 24 mgm per 100 c c after a five mile run in 29 5 minutes, at this time there was a large amount of albumin and a trace of hemoglobin, detectable only by chemical methods, in the urine

The plasma hemoglobin concentration was highest at the end of exercise and gradually decreased to the normal level. The rate of fall was approximately the same as the rate of decrease of plasma hemoglobin following an intravenous injection of hemoglobin solution in normal individuals (Fig 1) (37, 79).

In two of the patients (Cases 2 and 3) the plasma hemoglobin was always normal being approximately 5 mgm per 100 c c or less, except after running. In Case 1 the plasma hemoglobin was normal on most occasions when no brisk walk had been undertaken (Table 5), on several other similar occasions, however, the plasma hemoglobin was found to be 10 to 20 mgm per 100 c c. In one instance in which the plasma of a control blood sample taken before exercise appeared very slightly hemolyzed, another sample of blood was drawn before the exercise and 20 minutes after this first one. The second sample of blood likewise showed slight hemolysis and quantitative measurements showed the hemoglobin of the two samples to be 13 and 11 mgm per 100 c c respectively which findings indicate that this slight hemoglobinemia was actually present in the circulating blood and did not result from hemolysis due to any faulty technique in obtaining the plasma samples.

### *Hemoglobinuria*

Hemoglobin was excreted in the urine for one to three hours in the attacks of hemoglobinuria completely studied (Table 5, Figs 1 and 2, Case Reports). In Case 1 the total urinary hemoglobin excretion varied from 3 mgm to 458 mgm in the five attacks in which the total excretion was measured (Table 5), the amount excreted was roughly proportional to the height to which the plasma hemoglobin increased (Table 5). In Case 2 the total urinary excretion of hemoglobin after a one and one-half mile run was 22 mgm (Fig 1). On another occasion when this patient ran two miles a single urine specimen voided one-half hour after the run contained 90 mgm of hemoglobin per 100 c c. In Case 3 there was no hemoglobinuria on one occasion of study after a five mile run which produced a hemoglobinemia of 27 mgm per 100 c c, 2 mgm of hemoglobin were excreted in the urine after another five mile run which produced a hemoglobinemia of 24 mgm per 100 c c and considerable albuminuria (see below).

TABLE 5  
Quantitative Studies of Plasma Hemoglobin and Bilirubin and Urine Hemoglobin and Protein during Attacks of March Hemoglobinuria  
in Case 1

DATE	NATURE OF STUDY	TIME	PLASMA FINDINGS		URINE FINDINGS			
			Hemoglobin, mgm per 100 cc	Bilirubin, mgm per 100 cc	Color	Concen- tration, mgm per 100 cc	Hemoglobin Output, grams	Protein*
1939 4/21	4 mile walk in 60 minutes	Before walk End of walk	(Dark red)		Normal Dark red	(++)	(++)	0 ++
5/25	3 mile walk in 45 minutes	Before walk End of walk	<5 210	2.8	Normal Dark red	1450	0.319	0 ++
7/7	2 mile walk in 25 minutes	Before walk End of walk 1½ hours after 5 hours after 10 hours after		1.6 3.0	Normal Orange Light red Normal Normal	0 6 29 0 0	0 0.001 0.006 0 0	0 ++ ++ ++ 0
8/30	2½ mile walk in 40 minutes	Before walk End of walk 1 hour after 2 hours after 3 hours after 4 hours after 21 hours after	67 43	1.9 3.7 2.2	Normal Red Dark red Normal Normal	0 117 1200 0 0	0 0.025 0.180 0 0	0 ++ ++ 0 0
10/4	2½ mile walk in 40 minutes	Before walk End of walk 2 hours after 2½ hours after	<5 74 32	1.8 2.8	Normal Red Red Normal	0 197 139 4	0 0.073 0.038 0.007	0 ++ ++ ++
11/13	2½ mile walk in 35 minutes	Before walk End of walk	<5 54	2.6	Normal Red	0 50	0 0.057	0 ++



12/4	2½ mile walk in 40 minutes	Before walk End of walk 1 hour after	<5 111	2 1	Normal Light red Dark red	0 24 296	0 0 008 0 083	0 ++ ++
12/5	3 mile walk in 40 minutes in slightly kyphotic posture	Before walk End of walk 1 hour after 2 hours after 3 hours after 7 hours after	46 33 8 <5 <5	2 8 2 8 2 3	Normal Light red Red Normal	0 18 82 0	0 0 007 0 032 0	0 ++ ++ ++ 0
12/6	3 mile walk in 40 minutes in moderately kyphotic posture	Before walk End of walk 20 minutes after 1 hour after 2 hours after	24 24	2 5	Normal	0 0	0 0	0 +
12/7 (a m)	1½ mile walk in 30 minutes in normal posture	Before walk End of walk 1 hour after 2 hours after 3 hours after	10 35		Normal Normal Reddish	Trace 13 0	Trace 0 003 0	++ ++ ++ ++ 0
12/7 (p m)	3 mile walk in 40 minutes	Before walk ½ hour after			Normal Dark red	0 (++)	0 (++)	0 ++
1040 6/24	3 mile walk in 40 minutes†	Before walk End of walk	17 12	1 7 1 7	Normal Normal	0 0	0 0	0 0
7/8	4 mile walk in 60 minutes	Before walk End of walk ½ hour after	<5 38		Normal Brownish red Reddish	0 67 12	0 0 007 0 004	0 ++ ++
1011 1/8	6 3 mile walk in 90 minutes	Before walk End of walk ½ hour after	<5 20 13	1 9	Normal Normal	0 Trace	0 Trace	0 ++

\* These figures refer to results of qualitative nitric acid test for urinary protein

† This urine specimen was not collected

‡ Note that no attack was produced

TABLE 5  
Quantitative Studies of Plasma Hemoglobin and Bilirubin and Urine Hemoglobin and Protein during Attacks of March Hemoglobinuria in Case 1

DATE	NATURE OF STUDY	TIME	PLASMA FINDINGS		URINE FINDINGS			
			Hemoglobin, mgm per 100 cc	Bilirubin, mgm per 100 cc	Color	Hemoglobin Concentration, mgm per 100 cc	Hemoglobin Output, grams	Protein*
1939 4/21	4 mile walk in 60 minutes	Before walk End of walk	(Dark red)		Normal Dark red	(++)	(++)	0 ++
	3 mile walk in 45 minutes	Before walk End of walk	<5 210	2 8	Normal Dark red	1450	0 319	0 ++
	2 mile walk in 25 minutes	Before walk End of walk 1½ hours after 5 hours after 10 hours after		1 6 3 0	Normal Orange Light red Normal Normal	0 6 29 0 0	0 0 001 0 006 0 0	0 ++ ++ ++ 0
8/30	2½ mile walk in 40 minutes	Before walk End of walk 1 hour after 2 hours after 3 hours after 4 hours after 21 hours after		1 9 67 43	Normal Red Dark red + Normal Normal	0 117 1200 0 0 0	0 0 025 0 180 0 0 0	0 ++ ++ ++ 0 0
	2½ mile walk in 40 minutes	Before walk End of walk 2 hours after 2½ hours after	<5 74 32	3 7 2 2	Normal Red Red Normal	0 197 139 4	0 0 073 0 038 0 007	0 ++ ++ ++ +
	2½ mile walk in 35 minutes	Before walk End of walk	<5 54	2 6	Normal Red	0 50	0 0 057	0 ++

In Cases 1 and 2 pink to red urines were voided after exercise which produced plasma hemoglobin levels as low as 35 and 75 mgm per 100 c.c. respectively. On the other hand when hemoglobin solutions are injected intravenously in normal individuals hemoglobinuria does not occur at levels of plasma hemoglobin of less than somewhat over 100 mgm per 100 c.c. and may not occur at levels of even 200 mgm per 100 c.c. (37-79). To discover whether this difference was

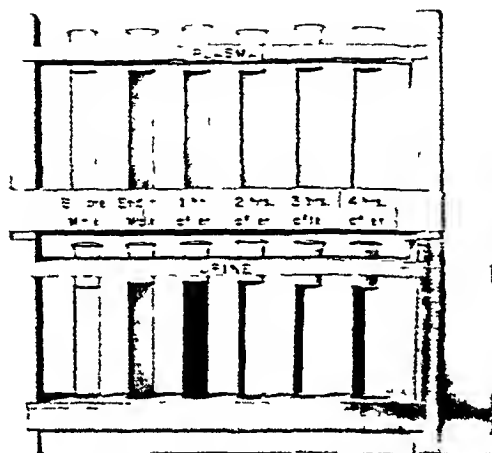


FIG. 2. COLOR PHOTOGRAPH SHOWING CLEAR, CHANGING DISCOLORATION OF URINE AND OF PLASMA DURING A TYPICAL ATTACK OF MARCH HEMOGLOBINURIA. PATIENTS WERE S + 2, MADE WALK IN 40 MINUTES IN CASE 1. THE PLASMA AT THE END OF THE WALK CONTAINED 61 MG. OF HEMOGLOBIN PER 100 C.C. THE MOST DARK RED URINE VOIDED ONCE VOIDED ONE HOUR AFTER THE END OF THE WALK CONTAINED 1200 MG. OF HEMOGLOBIN PER 100 C.C. THE VOLUME OF THIS URINE SPECIMEN WAS ONLY 15 C.C. SO THAT THE TOTAL HEMOGLOBIN EXCRETED IN THE SPECIMEN WAS ONLY 180 MG.

dependent upon conditions produced by the attack itself or whether hemoglobinuria might occur at similarly low levels of plasma hemoglobin in cases of march hemoglobinuria regardless of how it was produced an intravenous injection of hemoglobin solution sufficient in amount to produce a plasma hemoglobin concentration of 50 mgm per 100 c.c. was administered in Case 1. Hemoglobinuria occurred after this injection (Fig. 1) although the plasma hemoglobin concentration was less than half the lowest level observed to produce hemoglobinuria in normal individuals.

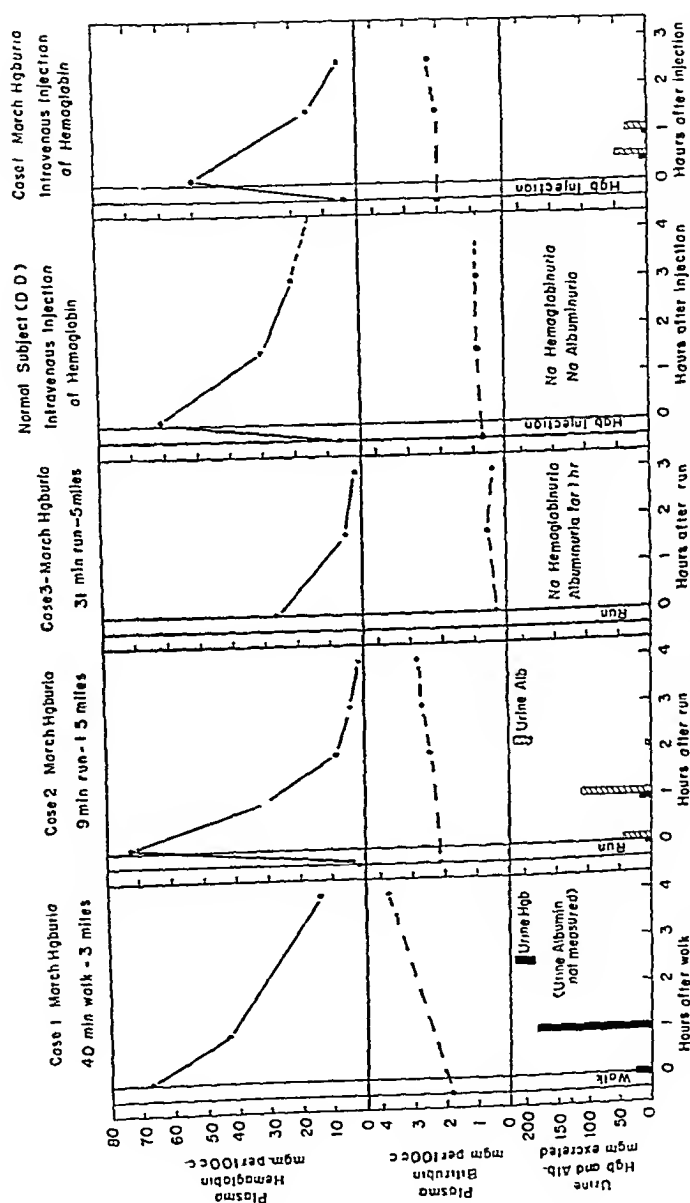


FIG. 1. THE PLASMA HEMOGLOBIN AND BILIRUBIN CONCENTRATIONS AND THE URINARY OUTPUT OF HEMOGLOBIN AND ALBUMIN DURING ATTACKS OF MARCH HEMOGLOBINURIA IN THE THREE CASES OF THIS STUDY, COMPARED WITH THE FINDINGS AFTER INTRAVENOUS INJECTIONS OF HEMOGLOBIN SOLUTION IN A NORMAL INDIVIDUAL AND IN ONE OF THESE CASES OF MARCH HEMOGLOBINURIA.

Case 3 the bilirubin increased less than 0.2 mgm per 100 c c one and one-half hours after a run in which the plasma hemoglobin was elevated to 27 mgm per 100 c c (Fig 1). The plasma bilirubin increases of from 0.5 to 1.8 mgm per 100 c c in Cases 1 and 2 following hemoglobinemia of 46 to 75 mgm per 100 c c produced by exercise were distinctly greater than the bilirubin increases of 0.1 to 0.2 mgm per 100 c c observed following hemoglobinemia of a similar extent in normal individuals after the intravenous injections of hemoglobin in solution and were of approximately the same order of increase as observed in patients with cholelithiasis, cirrhosis of the liver, or severe

TABLE 6  
*Excretion of Urobilinogen in Urine and Stool of Case 1*

DATE 1939	UROBILI- NOGEN OF URINE, MGM PER DAY	UROBILI- NOGEN OF STOOL, MGM PER DAY	REMARKS
September 26-27 inclusive		133	No attacks of hemoglobinuria
October 1-3 inclusive		106	No attacks of hemoglobinuria
October 4-6 inclusive		156	Attack of hemoglobinuria on October 4
December 2	2.3		No attack of hemoglobinuria
December 3	3.8		No attack of hemoglobinuria
December 4	0.8		Attack of hemoglobinuria
December 2-5 inclusive		132	Two attacks of hemoglobinuria, one on December 4, and the other on December 5

congestive heart failure (37, 80) after similar degrees of hemoglobinemia had been induced by intravenous injections of hemoglobin in solution. This observation is interpreted as demonstrating decreased bilirubin excretory rate in these 2 cases, also demonstrated following injection of bilirubin intravenously according to Weech's test (45) in one of these (Case 1).

#### *Urobilinogen Excretion*

The urinary urobilinogen output in Case 1 was normal both on days when no attack of hemoglobinuria occurred and on a day when an attack occurred (Table 6). The stool urobilinogen output was likewise within normal limits both in periods of study when no attack of

In Case 3 a urine of normal color but which contained 3 mgm of hemoglobin per 100 c c was voided after a run producing a plasma hemoglobin level of 24 mgm per 100 c c. Similarly in Case 1 a urine of normal color but which contained an immeasurable trace of hemoglobin giving a faintly positive benzidine test was voided after a 6.3 mile walk which produced a plasma hemoglobin of 20 mgm per 100 c c. That small traces of hemoglobin appeared in the urine at these low levels of plasma hemoglobin in the presence of considerable albuminuria due to exercise (11, 51) accords with our previous finding that traces of hemoglobin escape into the urine when low levels of plasma hemoglobin are induced by intravenous injections of hemoglobin solutions in patients with pre-existent albuminuria resulting from congestive heart failure (37).

### *Bilirubinemia*

The concentration of bilirubin in the plasma was elevated above normal at all times in two of the cases (Cases 1 and 2). In Case 1 the bilirubin concentration of the plasma on occasions other than during or shortly after attacks of hemoglobinuria varied from 1.7 to 3.0 mgm per 100 c c (Table 5), the values in Case 2 varied from 1.6 to 3.5 mgm per 100 c c. The bilirubin of Case 3 was normal, being 0.3 mgm per 100 c c. The Van den Bergh reaction was indirect in all cases. The bilirubin excretion test performed in Case 1 according to the method of Weech (45) showed a distinctly decreased excretory rate for bilirubin, the velocity constant for the disappearance of bilirubin being  $0.55 \times 10^{-3}$  mgm units as compared with values of over  $2.0 \times 10^{-3}$  found in normal individuals (45).

In all three cases the plasma bilirubin gradually increased after exercise producing hemoglobinemia, reached a peak in three to five hours and subsequently gradually returned to the control level (Table 5, Fig. 1). In three experiments in Case 1 in which the plasma hemoglobin increased to from 46 to 74 mgm per 100 c c and hemoglobinuria occurred following a walk, the bilirubin increased 0.5 to 1.8 mgm per 100 c c above the pre-exercise level. In Case 2 the bilirubin increased above the control level by 0.6 mgm per 100 c c in the four hours after a run which produced hemoglobinuria and a plasma hemoglobin concentration of 75 mgm per 100 c c (Fig. 1). In

The above calculations based on the quantitative plasma and urine hemoglobin findings demonstrate that the red cell mass hemolyzed intravascularly during the attacks of hemoglobinuria was small. Further, the findings of the absence of change in the hematocrit and blood hemoglobin values during attacks (Table 3) (27) together with the finding of normal urobilinogen excretion<sup>10</sup> in the stool during periods of study in which one or two attacks of hemoglobinuria occurred in Case 1 (Table 6) afford no evidence that any appreciable amount of blood was destroyed extravascularly, i.e., in such a manner that the hemoglobin was not released into the plasma. The very slight and transient increase in plasma bilirubin of Case 3 following a run producing hemoglobinemia (Fig. 1) also is evidence against the occurrence during attacks of any appreciable hemolysis in addition to that giving rise to the hemoglobinemia. The finding that the increases in plasma bilirubin concentration following attacks in the patients with chronic hyperbilirubinemia (Cases 1 and 2) were larger than occur in normal individuals following a similar degree of hemoglobinemia induced by intravenous hemoglobin injections is interpreted as due to decreased rate of excretion of the bilirubin derived from the hemoglobin released into the plasma during the attacks, and not as due to additional extravascular hemolysis. The absence of chronic hemoglobinemia, of anemia and of reticulocytosis in these cases, and the normal fecal urobilinogen output of Case 1 afforded furthermore no evidence of abnormal total blood destruction in the absence of attacks.

The relatively small amounts of blood usually hemolyzed during attacks and the infrequency with which the attacks occur in patients with march hemoglobinuria explain the absence of anemia in cases with this syndrome.

#### RENAL FUNCTION STUDIES

Urine analyses in the absence of attacks showed completely normal findings in all three cases. There was no albumin in the urine, the sediment was normal and the specific gravities were variable, with high values on one or more occasions in each case.

<sup>10</sup> The amount of blood destroyed intravascularly during an attack obviously would not be sufficient to produce a definite increase above normal in the fecal urobilinogen excretion for a three or four day period.

hemoglobinuria occurred and in periods which included attacks of hemoglobinuria (Table 6)

### *The Amount of Blood Hemolyzed During Attacks*

From the values of the plasma hemoglobin concentration at the end of exercise and the plasma volume<sup>9</sup> the total amount of hemoglobin released from red cells during the attacks of hemoglobinuria has been estimated. It is assumed that all of the hemoglobin released is present in the plasma at the end of exercise. The rate of disappearance of hemoglobin from the plasma is sufficiently slow to allow this assumption, the amount of hemoglobin excreted by the kidney during the period of exercise in these cases is insignificant in this connection, amounting to from 0.001 gm to 0.319 gm (Table 5, Fig 1), i.e., the hemoglobin equivalent of approximately 0.003 to 1.0 c.c. of red cells. It is assumed that intravascular hemolysis ceased on termination of the exercise since the plasma hemoglobin decreased after attacks at the same rate as after a single intravenous injection of hemoglobin solution producing a similar amount of hemoglobinemia in normal individuals (Fig 1) (37).

In attacks of hemoglobinuria in Case 1 in which the plasma hemoglobin at the end of exercise varied from 35 to 210 mgm per 100 c.c. calculations according to the above considerations show that from 1.0 to 6.3 gm of hemoglobin were liberated into the plasma. This corresponds to the hemoglobin of from 6 to 40 c.c. of the patient's blood, or approximately half this volume of red cells. Similarly in Case 2 in whom the plasma hemoglobin was 75 mgm per 100 c.c. at the end of a run it is estimated that 2.5 gm of hemoglobin were released, corresponding to the hemoglobin of approximately 16 c.c. of blood or 8 c.c. of cells.

### *Comment*

The total amount of hemoglobin excreted in the urine during the period of hemoglobinuria was always less than 10 per cent of the total amount of hemoglobin released into the plasma (Fig 1, Table 5)

<sup>9</sup> The blood volume was estimated from the average normal values, according to surface area, as given by Gibson and Evans (81), the plasma volume was then estimated from this calculated value for blood volume and the hematocrit value.



be "albumin (Table 7) "Albuminuria" also occurred during hemoglobinuria produced by an intravenous hemoglobin injection in Case 1 (Table 7)

The effect of attacks of march hemoglobinuria on the urea clearance was measured on two occasions. The urea clearance in the absence of attacks was normal and the production of hemoglobinuria by brisk walks did not alter the clearance (Table 8)

In other cases of march hemoglobinuria albuminuria has also been reported to occur following exercise insufficient to produce hemo-

TABLE 8  
*Studies of Effects of Attacks of Hemoglobinuria or Urea Clearance of Case 1*

DATE	TIME	ACTIVITY	URINE VOLUME CC. PER MIN.	UREA CLEARANCE, PER CENT NORMAL	REMARKS
12/4/39	8 20A-9 30A	Sitting	0 38	134 (S)*	
	9 30A-10 11A	Sitting	2 37	91 (M)	
	10 11A-11 00A	Lying	1 53	83 (S)	
	11 00A-11 55A	Lying	1 53	94 (S)	
	11 55A-1 15P	Standing	0 96	74 (S)	
	1 30P-3 00P	40 minute brisk walk	0 35	93 (S)	Hemoglobinuria
	3 10P-4 20P	Sitting	0 40	131 (S)	Hemoglobinuria
12/5/39	9 20A-10 05A	Sitting	0 42	92 (S)	
	10 05A-10 56A	40 minute brisk walk	0 77	131 (S)	Hemoglobinuria
	10 56A-12 05P	Sitting	0 57	136 (S)	Hemoglobinuria

\* "S" signifies standard clearance, "M" signifies maximum clearance

globinuria (2, 19, 24, 26) Schellong (19) reported that a small amount of a yellowish sediment, detected microscopically and which he believed contained hemoglobin pigment, appeared even before the albuminuria after exercise in his patient. The absence of albuminuria at rest or on standing in our patients accords with reported findings. Rosenthal (10) and Schellong (19) noted small urine volumes in their cases during the period of hemoglobinuria, the urine volumes in our cases during attacks varied from 0.2 c.c. per minute to 2.50 c.c. per minute. Studies of the urea clearance have not been reported in other cases.

The nitric acid, and heat and acetic acid tests for albumin were strongly positive in all the urine specimens containing hemoglobin. On some occasions protein continued to be excreted in the urine in small amounts for about an hour after hemoglobin excretion ceased (Table 5, Fig 1). In two instances (Cases 1 and 3) proteinuria occurred after exercise which produced slight hemoglobinemia but

TABLE 7

*Quantitative Studies of Albuminuria during Attacks of Hemoglobinuria in Cases of This Study*

CASE	DATE	TIME	URINARY FINDINGS		
			Total protein, mgm per 100 cc.	Hemo- globin, mgm per 100 cc.	"Albu- min," mgm per 100 cc.
1	12/5/39	Before walk	0	0	0
		End of 3 mile walk in 40 minutes	64	18	46
		1 hour after walk	171	82	89
	7/17/40	Before intravenous injection of hemoglobin in solution	0	0	0
		$\frac{1}{2}$ hour after injection	82	12	70
		1 hour after injection	28	3	25
		1 $\frac{1}{2}$ hours after injection	0	0	0
	1/8/41	Before walk	0	0	0
		End of 6.3 mile walk in 90 minutes	342	1	341
2	2/2/40	Before run	0	0	0
		End of 1 $\frac{1}{2}$ mile run in 9 minutes	332	43	289
		1 hour after run	272	34	238
		2 hours after run	9	0	9
3	10/17/40	End of 5 mile run in 30 minutes	148	3	145

no hemoglobinuria (Table 5, Fig 1). At the end of the one and one-half mile and five mile runs the urinary sediments of the two runners showed occasional white blood cells, rare casts, and rare red blood cells. Quantitative measurements of the total protein of the urine voided during attacks of hemoglobinuria (Cases 1 and 2) showed higher concentrations of total protein than of hemoglobin as measured by the benzidine method, the hemoglobin value was subtracted from that of the total protein and the remaining protein was considered to

findings do not conform however to the heretofore described instances of familial non-hemolytic jaundice in which splenomegaly and hepatomegaly have been lacking (82). The diagnosis of familial hemolytic jaundice is excluded by the normal hematological findings in both the brother and the sister as well as by the normal fecal urobilinogen excretion of the brother (Case 1). The possibility of cirrhosis of the liver in Case 1 cannot be excluded entirely.

The apparent increase in the size of the spleen and liver during attacks of march hemoglobinuria in Case 1 and of the liver in Porges and Strisower's (13) patient may be a result of the hemolytic attack and unassociated with the etiology of the attack. The spleen and liver in Case 1 remained as large for some hours after the attack as they were at the end of exercise although hemolysis stopped with the termination of exercise. In attacks of hemoglobinuria in blackwater fever (83), in paroxysmal hemoglobinuria due to chilling (40), and in favism (71), the spleen and liver also enlarge. The fact that the spleen and liver were palpable before exercise in Case 1 may have facilitated detection of the change after exercise. In the other cases of this study these organs were not palpable before or during attacks of hemoglobinuria.

#### THE INFLUENCE OF POSTURE DURING EXERCISE ON THE PRODUCTION OF ATTACKS OF MARCH HEMOGLOBINURIA

##### *Studies in the Cases of This Report*

All three cases of this study noted attacks of hemoglobinuria only after brisk walking (Case 1) or strenuous running for considerable distances (Cases 2 and 3) and never after any other physical activities. Studies were made to define more clearly the conditions necessary for production of the attacks of hemoglobinuria.

In one athlete who developed hemoglobinuria after runs of one and one-half miles in nine minutes (Case 2) the plasma hemoglobin was not elevated after a walk of three and one-half miles in 45 minutes and no hemoglobin or albumin appeared in the urine. In Case 3 the plasma hemoglobin was normal and no hemoglobinuria or albuminuria occurred after a bicycle ride of some four miles in approximately 45 minutes.

INCIDENCE AND SIGNIFICANCE OF JAUNDICE, SPLENOMEGALY, AND  
HEPATOMEGALY IN MARCH HEMOGLOBINURIA

Although chronic mild jaundice and hyperbilirubinemia were present in two of the cases (Cases 1 and 2) of this series, this finding is not characteristic of march hemoglobinuria for only one other case with slight jaundice (12) has been reported. No plasma bilirubin value was reported in this latter case (12). Plasma bilirubin values in four other reported cases (23, 26, 27, 31) were normal.

Evidences that the bilirubin excretory rate in Cases 1 and 2 of our series was decreased are presented above. The bromsulfalein excretion was normal in Case 1. Porges and Strisower (13) and Witts (27) have reported increased urobilinogen excretion in the urine following attacks, quantitative values are not given. Quantitative studies in Case 1 of our series revealed normal urinary urobilinogen excretion both in the absence of and during attacks. There was no bile in the urine at any time in the three cases of our series.

In Case 1 of the present study the spleen and liver were palpable both before and after attacks and appeared enlarged on X-ray examination. A palpable spleen has not been noted in any reported cases of march hemoglobinuria, slight enlargement of the liver in the absence of an attack has been reported in only one case (19), in another reported case (13) the liver became palpable after a period of several days during which daily attacks of march hemoglobinuria had been precipitated.

These findings of moderate hepatomegaly and splenomegaly in one of the cases reported here (Case 1) and of mild jaundice in two of these (Cases 1 and 2) are, accordingly, unusual in march hemoglobinuria. The chronic hepatomegaly and splenomegaly in Case 1 cannot be ascribed to the repeated attacks of hemolysis since other patients with march hemoglobinuria who have had more frequent attacks over a long period of time do not show chronic enlargement of these organs. The sister, the only sibling of this patient (Case 1), on two examinations six months apart, showed slightly increased plasma bilirubin values, i.e., 1.1 and 1.5 mgm per 100 cc, the plasma hemoglobin on both occasions was normal. This finding of slight hyperbilirubinemia in the sister suggests a familial tendency toward jaundice. The

findings do not conform, however, to the heretofore described instances of familial non-hemolytic jaundice in which splenomegaly and hepatomegaly have been lacking (82). The diagnosis of familial hemolytic jaundice is excluded by the normal hematological findings in both the brother and the sister as well as by the normal fecal urobilinogen excretion of the brother (Case 1). The possibility of cirrhosis of the liver in Case 1 cannot be excluded entirely.

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In Case 1 the significance of the history of bicycling for considerable distances without development of hemoglobinuria was tested by means of ergometric studies. It was desired to establish whether the intensity of exertion rather than the type of exercise might be the controlling factor in the production of attacks. Experiments<sup>11</sup> were done on the bicycle ergometer in which the load was so adjusted that the oxygen consumption during riding was at first approximately the same and then considerably greater than that during walking which produced hemoglobinuria. After 25 minutes of work on the bicycle, during which time the average pulse rate was 112 beats per minute and the oxygen consumption was 1.10 liters per minute, the urine showed no hemoglobin or albumin (Table 9). After collection of the urine specimen the patient returned immediately to the bicycle and continued work with a greater load for 14 more minutes, during which the pulse rate rose to 160 beats per minute and the oxygen consumption to 1.65 liters per minute. The patient became very tired and perspired profusely. A blood sample drawn at the end of this work showed less than five mgm of hemoglobin per 100 c.c. and the urine showed no hemoglobin or albumin. A half hour after this exercise on the bicycle the patient took a 35 minute brisk walk of two and one-half miles at the end of which he passed a red urine containing 50 mgm of hemoglobin per 100 c.c. The plasma was red and contained 54 mgm of hemoglobin per 100 c.c. The average pulse rate during this walk was 86 beats per minute, the patient was not tired, nor was he perspiring at the end of the walk.

These controlled experiments showed that work of a greater extent and longer duration than that necessary to produce hemoglobinuria on walking could be performed on the bicycle without any evidence of abnormal hemolysis whatsoever. The possible importance of body position during work for the production of hemolysis in this case was suggested by this observation. Accordingly, the effectiveness of body position alone and of body position during walking in the production of hemolysis was tested. Standing still in the upright position for one hour and for one and one-quarter hours produced no hemolysis (Table 9). In three experiments no hemolysis occurred when the patient lay

<sup>11</sup> We are grateful to Dr. D. B. Dill through whose kindness and helpful assistance the experiments on the bicycle ergometer and treadmill were made possible.

TABLE 9

*Studies of the Effectiveness of Bed Rest, of Various Body Postures Alone, and of Walking in Various Postures on the Production of Attacks of Hemoglobinuria in Case 1*

DATE	CONDITION OF STUDY	DURATION OF EXERCISE MINS., MINUTES	HEART RATE MINUTE	OXYGEN CONSUMPTION LITERS PER MINUTE	BLOOD LACTIC ACID AT END OF EXERCISE, MG. PER 100 CC.	CLARKE HEMOGLOBIN AT END OF EXERCISE, MG. PER 100 CC.	URINE HEMOGLOBIN	URINE PROTEIN*
11-15	Work on a cycle ergometer with load of 3.5 kg.	25	112	1 10	—	—	0	0
	Continuation of work on a cycle with load of 3.5 kg.	15 5	160	1 65	47	<5	0	0
	2.5 mile walk in normal up- right posture $\frac{1}{2}$ hour after end of ride	35	86	—	—	54	—	—
12-4	Sitting in bed	180				<5	0	0
	Lying in bed on back	60				<5	0	0
	Lying in bed on back in forced kyphotic posture	60				<5	0	0
	Standing still in normal up- right posture	75				<5	0	0
	2.75 mile walk in normal up- right posture	40				111	—	—
12-5	5 mile walk in slightly ky- photic posture	40				46	—	—
12-6	3 mile walk in moderately kyphotic posture	40				24	0	—
12-7	Walk on treadmill in mod- erate kyphotic posture	30	170	1 75	30	107	0	0
	Walk on treadmill in normal posture $\frac{1}{2}$ hour later	30	120	1 15	17	35	—	—
12-8	Standing still in normal up- right posture	60				<5	0	0
	Lying on back on table in markedly forced kyphotic posture	40				<5	0	0

\* These figures refer to results of qualitative nitro and test for urinary protein.

† The plasma of two blood samples drawn during the half hour before this exercise was started contained 15 and 11 mgm. of hemoglobin per 100 cc., so that there was no rise above the control during the exercise.

In Case 1 the significance of the history of bicycling for considerable distances without development of hemoglobinuria was tested by means of ergometric studies. It was desired to establish whether the intensity of exertion rather than the type of exercise might be the controlling factor in the production of attacks. Experiments<sup>11</sup> were done on the bicycle ergometer in which the load was so adjusted that the oxygen consumption during riding was at first approximately the same and then considerably greater than that during walking which produced hemoglobinuria. After 25 minutes of work on the bicycle, during which time the average pulse rate was 112 beats per minute and the oxygen consumption was 1.10 liters per minute, the urine showed no hemoglobin or albumin (Table 9). After collection of the urine specimen the patient returned immediately to the bicycle and continued work with a greater load for 14 more minutes, during which the pulse rate rose to 160 beats per minute and the oxygen consumption to 1.65 liters per minute. The patient became very tired and perspired profusely. A blood sample drawn at the end of this work showed less than five mgm. of hemoglobin per 100 c.c. and the urine showed no hemoglobin or albumin. A half hour after this exercise on the bicycle the patient took a 35 minute brisk walk of two and one-half miles at the end of which he passed a red urine containing 50 mgm. of hemoglobin per 100 c.c. The plasma was red and contained 54 mgm. of hemoglobin per 100 c.c. The average pulse rate during this walk was 86 beats per minute, the patient was not tired, nor was he perspiring at the end of the walk.

These controlled experiments showed that work of a greater extent and longer duration than that necessary to produce hemoglobinuria on walking could be performed on the bicycle without any evidence of abnormal hemolysis whatsoever. The possible importance of body position during work for the production of hemolysis in this case was suggested by this observation. Accordingly, the effectiveness of body position alone and of body position during walking in the production of hemolysis was tested. Standing still in the upright position for one hour and for one and one-quarter hours produced no hemolysis (Table 9). In three experiments no hemolysis occurred when the patient lay

<sup>11</sup> We are grateful to Dr. D. B. Dill through whose kindness and helpful assistance the experiments on the bicycle ergometer and treadmill were made possible.



Experiments were performed in Case 1 and in two normal individuals to discover whether hemolysis might occur locally when exercise of the hand was performed in the presence of stasis of the venous blood of the arm. A blood pressure cuff was applied to the arm above the elbow and pressures of from 45 to 200 mm. of mercury imposed in



FIG. 3. PHOTOGRAPH SHOWING THE MODERATELY KYPHOTIC POSTURE IMPOSED BY THE REMOVABLE PLASTER JACKET IN WHICH THE PATIENT (CASE 1) WALKED FOR 30 MINUTES ON THE TREADMILL WITHOUT PRODUCTION OF AN ATTACK OF MARCH HEMOGLOBINURIA.

various experiments. The exercise was performed by forcibly opening and closing the hand or by rapid intermittent squeezing of a rubber bulb in the hand to the point of pain and exhaustion of the muscles. In three experiments in two normal individuals pressures of 45 to 55 mm. of mercury were applied. In two of the three experiments the tourniquet was applied for 10 to 12 minutes before starting the exer-

on his back for 40 to 60 minutes in the normal posture or in a lordotic posture imposed by propping the small of the back (Table 9). On the days when these studies were made a hemolytic attack could always be produced when the patient walked in the normal position for 30 minutes or more.

The effect of body position during walking in Case 1 was tested by noting the effects of imposing a slightly or moderately kyphotic posture by means of removable plaster jackets.<sup>12</sup> With the plaster jacket producing a very slightly kyphotic position a walk of three miles in 40 minutes still produced hemoglobinemia and hemoglobinuria. The extent of hemolysis due to this walk, however, was less than that which had occurred on the previous day on a similar walk with no jacket (Table 9). On the day following this walk in the slightly kyphotic position, a plaster jacket which imposed a somewhat greater kyphosis (Fig. 3) was applied and the same walk was undertaken. On this occasion no hemoglobinuria resulted and the plasma hemoglobin rose to only 24 mgm per 100 c.c. compared with 46 mgm with the first jacket and 111 mgm with no jacket (Table 9).

A further and more convincing demonstration of the effect of posture on the development of hemolysis on walking was obtained by treadmill experiments in which the oxygen consumption was measured during two walks of 30 minutes each, one in the moderately kyphotic position with the plaster jacket (Fig. 3), and the other without the jacket. No hemoglobinemia or hemoglobinuria resulted from the 30 minute walk in the moderately kyphotic position, whereas an increase in the plasma hemoglobin to 35 mgm per 100 c.c. and hemoglobinuria resulted from a walk of the same duration with the same speed of the treadmill in the normal upright posture (Table 9). In this latter experiment a load of the same weight as the jacket was carried on the back. The oxygen consumption in the kyphotic posture during exercise on the treadmill was 1.78 liters per minute, in the normal upright position 1.15 liters per minute.

The above finding that hemolytic attacks in Case 1 could be prevented by imposing the kyphotic position during the walk, and other considerations discussed below, suggested the possibility that stasis of blood during exercise might be the cause of the hemolytic attack.

<sup>12</sup> We are indebted to Dr. Robert Ulin for orthopedic advice and for making these jackets.

of the lumbar spine have been reported (13 19, 27 31) most cases as those of the present study have no postural abnormalities Fisher and Bernstein (31) have commented on the exaggerated lordotic posture assumed by their patient while running.

Porges and Strisower (12 13) reported a case in which attacks of hemoglobinuria occurred after one-quarter hour of fast walking in the usual upright position but did not occur after strenuous walking for several hours in the kyphotic position Schellong (19) also reported a case in which an attack did not develop when the patient walked in the kyphotic position In two patients studied by Foerster (17) in Oehme's (21) patient, and in Witts (27) patient no effect of posture on the development of attacks could be demonstrated No hemoglobinuria has been produced in cases with this syndrome by standing still in the upright or in a forced lordotic posture (Case 1) (12 13 18 19) or by lying in a forced lordotic posture (Case 1) (12) even when the legs were moved as though walking (12) Albuminuria did occur on standing still in two reported cases (12 14) In Case 1 of our study it was also demonstrated that no hemoglobinemia was produced by still standing or by lying in a forced lordotic posture The experiments on the bicycle ergometer and the treadmill in Case 1 of our series (Table 9) demonstrated conclusively the effect of posture on the production of hemoglobinuria during exercise It is interesting that although runs of only one and one-half miles in nine minutes caused frank attacks of hemoglobinuria in Case 2 a walk of 3.5 miles in 45 minutes failed to produce any hemoglobinemia whether a difference in posture during these exercises was of importance was not established

#### CRITICAL REVIEW OF THEORIES REGARDING THE ETIOLOGY OF MARCH HEMOGLOBINURIA

The absence of any uniform abnormalities in cases of march hemoglobinuria the absence of any characteristic symptoms during attacks the fact that the condition is benign so that autopsy studies are not available and the failure to find autohemolysis in the plasma or thus far abnormalities of the red cells either during or in the absence of attacks in patients with this syndrome make the discovery of the etiology of attacks most difficult Several theories concerning the mechanism of hemolysis have been proposed, but thus far satisfactory

cise The duration of the exercise varied from two and one-half to six and one-half minutes During the first two and one-half to three minutes after completion of the exercise and without removal of the tourniquet five to seven samples of blood, each of 10 c c amounts, were withdrawn from the antecubital vein There was no visible hemolysis in any of the centrifuged samples, the plasma hemoglobin, as measured by the benzidine method, was not increased In Case 1 two similar experiments were performed A cuff pressure of 200 mm of mercury was applied in both instances In one experiment a blood sample was drawn four minutes after the end of three minutes of exercise, the pressure was then released for 10 pulsations, the cuff quickly re-inflated and another blood sample then withdrawn In the other experiment in this case, exercise of the hand was performed for three minutes, and five samples of blood, each of 10 c c, were withdrawn from the antecubital vein after gradually wrapping the arm from the hand to the elbow in an Esmarch bandage In this study, likewise, there was no visible hemolysis in any of the centrifuged blood samples, and quantitative measurements revealed no increase in the plasma hemoglobin concentration

It was thought that if red cells were trapped in the spleen due to venous stasis of the splenic vein during exercise that this might be reflected by a lowering of the hematocrit Studies in two of our patients revealed no lowering of the hematocrit following exercise which produced an attack of hemoglobinuria and therefore afforded no evidence in support of this concept (Table 3)

### *Comment*

The apparent effect of posture during exercise on the production of attacks of march hemoglobinuria was first suggested by the observations of Fleischer (1) who published the first case of this syndrome This author noted that attacks occurred in his case after a brisk walk of an hour's duration but did not occur when the patient split wood or pounded sugar strenuously for two to three hours Several other investigators have noted that in patients in whom attacks occurred on walking considerable amounts of exercise other than walking failed to produce attacks (2, 5, 7, 10, 12, 14, 16, 19)

Although rare cases of march hemoglobinuria with moderate lordosis

is no definite evidence however, that venous stasis occurs in the kidneys during attacks of march hemoglobinuria or that if stasis of blood in the renal veins did occur during a short walk or run that an attack of hemoglobinuria would result. Roentgen-ray examinations in two reported cases (27, 31) revealed no abnormal size, position or mobility of the kidneys, no pertinent renal abnormalities were revealed by X-ray or pyelographic studies in two of our cases (Case Reports). The urea clearance was not affected by attacks of hemoglobinuria in one of these cases (Case 1). The albuminuria which is associated with the hemoglobinuria of an attack of march hemoglobinuria is also observed during attacks of hemoglobinuria caused by injections of hemoglobin solutions intravenously in normal individuals (37). The albuminuria which occurs at times with walks just insufficient in duration to cause hemoglobinuria (Table 5) (2, 19, 24, 26) does not necessarily indicate renal venous stasis, for in abortive paroxysms of the syphilitic type of paroxysmal hemoglobinuria albuminuria has also been observed in the absence of hemoglobinuria but in the presence of hemoglobinemia (40).

Because of the apparent importance of the upright posture during exercise for the production of attacks of march hemoglobinuria and because a moderate lumbar lordosis is present in occasional patients with this syndrome it has been suggested that march hemoglobinuria and orthostatic albuminuria are closely related phenomena (31). However patients with typical orthostatic albuminuria do not have march hemoglobinuria and patients with march hemoglobinuria with rare exceptions, do not have albuminuria at rest even when standing or lying in the forced lordotic position. It is an important observation that cystoscopic examinations in patients with orthostatic albuminuria have revealed albumin only in the urine from the left kidney, presumably resulting from compression of the left renal vein against the aorta in the lordotic position (86, 87), whereas cystoscopic examinations in two cases of march hemoglobinuria have revealed hemoglobin in the urine from both kidneys (12, 19). Further the physiological albuminuria (11) and physiological intravascular hemolysis of very strenuous exercise (49) are not necessarily related phenomena for after such exercise albuminuria sometimes occurs in the absence of abnormal plasma hemoglobin values, and slight but

evidences of proof of these theories are lacking. The data of the present study define the condition more clearly than has been possible heretofore and prompt a critical discussion of some of the existing theories as to the site and mechanism of hemolysis.

It has been suggested (17, 26, 64) that march hemoglobinuria may be related to the paralytic type of "hemoglobinuria," now known as myoglobinuria, in which the muscle physiology is deranged. The spectrophotometric identification of the urinary pigment as hemoglobin and not myoglobin in Witts' (27) case of typical march hemoglobinuria who developed attacks on walking, and the identification of the plasma and urinary pigments as hemoglobin in the patient of the present study who developed attacks on walking (Case 1), and in one of the patients who developed attacks on running (Case 3), demonstrate conclusively that the pathologic physiology of march hemoglobinuria is entirely different from that of myoglobinuria.

Meyer (84), Witts (27), and Schellong (19, 85) have suggested that hemolysis takes place locally in the kidneys. It has been reasoned that since the general symptoms during an attack are trivial, jaundice is absent and the degree of hemoglobinemia appears to be relatively small, the hemolysis is probably confined to the vessels of the kidney, the major part of the released hemoglobin being excreted by the kidney as promptly as it is produced, with only a small amount passing into the general circulation. No quantitative urine hemoglobin findings were available until now, the quantitative data of the present study show that actually only a very small portion, usually much less than 10 per cent, of the hemoglobin liberated during an attack was excreted in the urine. Further, the observation that, after an intravenous injection of hemoglobin solution hemoglobinuria occurred in Case 1 of our series at a level of hemoglobinemia the same as that found during the hemoglobinuria of typical attacks produced by walking is strong evidence that the level of hemoglobinemia during the attacks was sufficient in this case to give rise to the hemoglobinuria. It is important in this connection too that hemoglobinemia of 24 and 27 mgm per 100 c.c. occurred in two of the cases of our study during exercise of an amount insufficient to produce any hemoglobinuria. Schellong (19) has advanced the theory that the hemolysis is produced by stasis of the renal veins owing to the lordotic posture in walking. There

toms developed although it was calculated that the hemoglobin from an average of 250 c c of the patient's blood was released daily into the plasma for five days. We have observed a case of hemoglobinemia with marked hemoglobinuria occurring in an acute hemolytic attack following sulfanilamide therapy in which there was a rise in temperature to 103°F, but chills were absent and there were no symptoms (90). These observations further illustrate that the lack of symptoms in the presence of hemoglobinemia and hemoglobinuria is not characteristic of march hemoglobinuria.

Several attempts have been made to produce hemolytic attacks in patients with march hemoglobinuria by means other than exercise. As noted above, no attack of hemoglobinuria has been produced by having the patient stand still in the upright position. Chilling of an extremity by immersion in ice water (Rosenbach test) for ten minutes has repeatedly failed to produce hemoglobinuria in patients with this syndrome. No local hemolysis occurred in Case 1 of our study when exercise of the hand was performed during venous stasis produced by a tourniquet on the arm. In view of Stormont's (91) observation that prolonged hyperventilation in dogs produced hemoglobinuria the effect of hyperventilation on the production of intravascular hemolysis was studied in Case 1 of our series. Hyperventilation for 20 minutes which produced numbness of the fingers, a positive Chvostek sign and an alveolar carbon dioxide content of 2.8 per cent failed to produce any hemoglobinemia. Injections of adrenalin (13, 19, 23), atropine (13), nitrites (13) and caffeine (13), roentgen ray irradiation of the spleen (19), diathermy of the spleen (13) and of both kidneys (19), and induction of fever by injection of killed typhoid bacilli (26) have failed to produce attacks in patients with march hemoglobinuria.

In most patients there is no history of an injury which might be pertinent in respect to the subsequent development of attacks. In Witts' case the patient fell from a ladder striking his abdomen with his knees a week before the attacks began (27). In one of our cases (Case 3) there was a history of hematuria of a few days' duration following a back injury resulting from a high dive six years before the first attack of march hemoglobinuria.

The results of the quantitative studies of plasma hemoglobin during

definite hemoglobinemia sometimes occurs in the absence of albuminuria (49)

Porges and Strisower (13) have suggested that the hemolysis in march hemoglobinuria does not occur intravascularly but occurs in the spleen. These authors have postulated the existence of an abnormal vasomotor reflex during walking in the lordotic position which reflex gives rise to an increased blood supply of the spleen and hence to increased hemolysis, with retention of the stromata by the spleen and liver and escape of abnormal amounts of hemoglobin into the blood stream. These authors (13) pointed out that evidence of splenic engorgement during attacks of march hemoglobinuria was lacking, but that one of them had observed in perfusion experiments increased hemolysis of the splenic blood after engorgement of the spleen (88). This theory (13) and the theory that hemolysis occurs in the kidney (19, 27, 84) with escape of much of the hemoglobin into the urine before it enters the general circulation attempt to explain both the apparent effect of posture during exercise in the production of attacks and the absence of chills, fever, and other symptoms which are associated with attacks of intravascular hemolysis in the syphilitic type of hemoglobinuria. It seems, however, unnecessary to postulate that hemolysis must occur outside the general circulation because symptoms are absent or trivial. Other hemolytic conditions in which hemolysis occurs intravascularly may be asymptomatic in the presence of even a greater degree of hemoglobinemia than usually occurs in an attack of march hemoglobinuria. In Marchiafava-Micheli disease attacks of hemoglobinuria with a high degree of hemoglobinemia may occur without associated chills or fever, and frequently with no other symptoms referable to the hemolysis (41, 64). It is of interest that Penfold and Robertson (89) produced intravascular hemolysis with marked hemoglobinuria in rabbits by injection of distilled water without causing fever, and concluded that the cause of the fever in attacks of paroxysmal hemoglobinuria of the syphilitic type is unknown. Other conditions may be cited in which there were no symptoms in the presence of hemoglobinemia which presumably resulted from hemolysis within the general circulation. In a case with an acute attack of marked hemoglobinemia and hemoglobinuria of obscure etiology recently studied in this laboratory (55) no chills, fever, or other symp-



may be the cause of hemolysis. We have been unable however to accumulate any proof that venous stasis occurs in any organ during attacks of march hemoglobinuria. Whether there is any relationship between the etiology of the attacks and the apparent enlargement of the spleen after an attack noted thus far in only one case of this syndrome (Case 1) or of the liver noted in only two cases (Case 1) (13) cannot be definitely stated, as noted above the occasionally observed increases in the size of these organs after an attack may be simply a result of the hemolytic attack. There is no definite evidence of stasis in the renal veins during an attack. It has recently been observed that when intravascular stasis in the spleen is maintained for several hours in dogs the splenic vein blood shows hemoconcentration, variable increases in the fragility of the red cells to hypotonic saline, and hemoglobinemia (92, 93, 94); also complete obstruction of the inferior vena cava for 2 hours in the dog produces a significant increase in the fragility of the red cells of the blood obtained from this site (93). It may be of significance in this respect that enlargement of the liver after long distance runs has been observed in poorly conditioned athletes (95). Occlusion of the renal artery and vein in the dog for two hours leads to a decrease in the osmotic resistance of the red cells of the renal vein blood (94). A slight increase in the red cell fragility of the capillary blood of the arm occurs in normal subjects when arrest of the circulation of the arm is maintained for 10 to 15 minutes (96), as reported above; however no hemoglobinemia resulted from similar stasis experiments during which exercise of the hand was performed by normal subjects or by a case of march hemoglobinuria. Any theory proposed to explain the hemolytic attack in march hemoglobinuria must be consistent with the facts that appropriate exercise of as short duration as nine minutes may be sufficient to cause a frank attack of hemoglobinuria and that hemolysis promptly ceases on termination of the exercise.

Further study both of intravascular hemolysis in normal subjects following severe exercise and of patients with march hemoglobinuria who develop attacks on short walks or moderate runs are required in order to obtain the necessary links to solve the problem of the etiology of this type of hemolysis.

attacks in our cases (Fig 1) (Table 5), the one measurement of plasma hemoglobin reported by Witts (27), and the finding of reddish plasma by other investigators (1, 11, 13, 14, 19, 26) during attacks demonstrate that hemoglobinuria in march hemoglobinuria occurs only in the presence of hemoglobinemia. It is evident further that hemoglobinuria occurs only above certain levels of hemoglobinemia since exercise sufficient to produce only slight hemoglobinemia produces no hemoglobinuria (Fig 1, Table 5). From these findings it is concluded that the hemoglobinuria is secondary to the hemoglobinemia. Why hemoglobinuria may be initiated at lower levels of plasma hemoglobin in cases with this syndrome after exercise (Fig 1, Table 5) (27) than in normal individuals after an injection of hemoglobin intravenously (37, 79) is not entirely clear. It was thought at first that this finding might be of significance in relation to the mechanism of the attack itself. However, the fact that hemoglobinuria occurred in Case 1 at a similarly low plasma hemoglobin level after intravenous injection of hemoglobin solution is strong evidence against this thought. In Marchiafava-Micheli disease it has been shown that hemoglobinuria may occur with plasma levels as low as those associated with hemoglobinuria in our cases (41), the situation in Marchiafava-Micheli disease is not closely analogous, however, since in this condition there is chronic hemoglobinemia and very frequent episodes of, or constant, hemoglobinuria (41). The factors concerned with the renal excretion of hemoglobin after intravenous injections of hemoglobin solutions in normal man and in animals have been discussed in some detail in an earlier paper (37).

The finding that posture during exercise is important in the production of attacks in many patients with march hemoglobinuria would seem to afford a lead to the solution of the problem of the mechanism of hemolysis. As noted above, standing still in the upright position and lying in a forced lordotic position have thus far failed to produce attacks. It appears that exercise, as well as assumption of an appropriate posture during the exercise is necessary to produce attacks. The present authors, like others, have been led to consider the possibility that there may be a venous stasis in one or more of the abdominal organs in the usual walking or running position in patients with this syndrome, and that the presence of this venous stasis during exercise

ported that attacks were prevented in his patient by the administration of cevitic acid. The patient may be assured that in most instances spontaneous recovery occurs after a period of months to a few years.

### SUMMARY AND CONCLUSIONS

1 Detailed clinical and laboratory studies are reported in three hitherto unpublished cases of march hemoglobinuria and a review of present knowledge concerning this condition is presented. The investigation has included hematological studies, a study of the diagnostic criteria, observations on blood pigment metabolism and on renal and hepatic function, and physiological investigations of the conditions necessary for the production of attacks.

2 In the three cases of this study the clinical findings conformed in most respects to those in previously reported cases of this condition. March hemoglobinuria is a form of paroxysmal hemoglobinuria which occurs in otherwise healthy young males following walking or running. There are usually no or only slight symptoms with attacks. Physical examination usually reveals no abnormalities; a lumbar lordosis in rare cases and slight enlargement of the liver in one case have been reported. In the three cases reported here physical examination revealed no abnormalities except mild icterus in two of the patients and moderate enlargement of the spleen and liver in one of these. Spontaneous recovery apparently occurs within a period of a few months to years.

3 Hematological studies in the cases reported here gave normal results; there was no anemia or reticulocytosis, the fragility of the red blood cells and the white blood cell and platelet counts were normal; tests for isohemolysins and autoagglutinins were negative. These results accord with the available observations in previously reported cases.

4 The diagnostic criteria which must be utilized in differentiating march hemoglobinuria from paroxysmal hemoglobinuria from chilling (syphilitic type) from chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli disease) from myoglobinuria and from favism are outlined.

5 Studies of the hemoglobin of the plasma and urine and of the

## COMMENTS ON THERAPY

As pointed out above, symptoms are lacking or trivial during attacks of march hemoglobinuria, blood destruction is relatively slight, no permanent damage to any organs has been shown to occur as a result of attacks, and apparent recovery usually occurs spontaneously. In the absence of proof that any damage results from attacks of hemoglobinuria in march hemoglobinuria, the management of cases becomes a matter of clinical judgment. The rather general opinion has been that the condition is a harmless abnormality and demands no very active treatment. There is no question, however, but that most patients with this syndrome are considerably perturbed by the passage of a red urine, even though they have been reassured by the physician. A review of the circumstances under which most patients develop attacks shows that attacks could be prevented without any great inconvenience to the patient by omission of some activity which he practices infrequently. After a careful study of a given case the patient can be advised as to what kind and extent of activity precipitates his attacks and he will frequently spontaneously avoid such activity.

Although no permanent damage apparently results from very infrequent and moderate attacks of march hemoglobinuria, the possibility that the more prolonged attacks of hemoglobinuria or that the very frequent attacks might lead to kidney or liver damage through precipitation of hemoglobin products cannot be dismissed. We believe, therefore, that measures should be taken to control the condition in any patient who has prolonged or very frequent attacks of hemoglobinuria. If the restriction of activity necessary to prevent attacks is so great as to interfere seriously with the patient's daily normal life, a study of the case may reveal that a brace inducing some measure of kyphosis will be of great benefit. In the event that attacks cannot be feasibly controlled by restriction of activity or by a brace, it is suggested that fluids should be forced moderately and sufficient alkali be administered to maintain an alkaline urine during the hours when the activity leading to hemoglobinuria is undertaken, this precaution is suggested to prevent precipitation of hemoglobin in the renal tubules, in accord with considerations discussed above. Hoffmann (29) re-

ported that attacks were prevented in his patient by the administration of cevitic acid. The patient may be assured that in most instances spontaneous recovery occurs after a period of months to a few years.

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5 Studies of the hemoglobin of the plasma and urine and of the

bilirubin of the plasma during attacks in these cases permit the following conclusions

- (1) Spectrophotometric analyses showed the plasma pigment during attacks to be oxyhemoglobin, and the urinary pigment to be mainly oxyhemoglobin
  - (2) Hemoglobinuria during the attacks lasted for from one to three hours
  - (3) *Hemoglobinuria is secondary to hemoglobinemia*, for hemoglobinuria is always associated with hemoglobinemia, whereas after somewhat less exercise than necessary to produce a frank attack hemoglobinemia may be present in the absence of hemoglobinuria
  - (4) The hemolysis leading to hemoglobinemia occurs during the exercise only, for hemoglobinemia is greatest at the termination of exercise and decreases gradually thereafter at a rate which accords with the rate expected for the disappearance of the hemoglobin present at the end of the attack
  - (5) The red cells of from only six to 40 c c of blood were destroyed intravascularly in the attacks of march hemoglobinuria studied in these cases
  - (6) The total amount of hemoglobin appearing in the urine during the entire attack represented less than 10 per cent of the amount freed into the plasma during the period of hemolysis
  - (7) Hemoglobinuria may occur at lower levels of plasma hemoglobin in an attack of march hemoglobinuria than has been observed in normal individuals after intravenous injections of hemoglobin in solution. In studies in one case of march hemoglobinuria, hemoglobinuria occurred at the same low level of plasma hemoglobin after intravenous injection of hemoglobin in solution as during an attack occasioned by exercise
  - (8) The plasma bilirubin gradually increased after exercise producing hemoglobinemia, reached a peak in two to five hours, and then gradually returned to the control level
- 6 The hematocrit and blood hemoglobin values which were normal in the absence of attacks of hemoglobinuria did not change during attacks
- 7 The fecal urobilinogen excretion measured in one case was

within normal limits in the absence of attacks of hemoglobinuria and also during periods when one or two attacks occurred

8 The findings afforded evidence that the blood destruction during attacks is entirely intravascular, i.e. that all of the hemoglobin from red cell destruction appears in the plasma giving rise to hemoglobinemia

9 The studies afforded no evidence of chronically increased blood destruction

10 Urine analyses in the absence of attacks showed completely normal findings in all three cases. The urea clearance studied in one case was normal in the absence of and during attacks. Albuminuria was observed after exercise which produced slight hemoglobinemia but no hemoglobinuria. Albumin was present in all urine specimens containing hemoglobin and on some occasions 'albumin' continued to be excreted in small amounts for about an hour after hemoglobin excretion had ceased

11 Studies of the factors required to precipitate attacks in the patients of this study afford the following information

- (1) Hemoglobinemia and hemoglobinuria were produced by short brisk walks or by fast runs
- (2) No hemoglobinemia was produced by standing still in the upright position for a prolonged period of time or by the prolonged assumption of a lordotic recumbent position
- (3) Studies of the oxygen consumption during work on the bicycle ergometer and treadmill in the patient who developed attacks of hemoglobinuria on walking demonstrated that if a moderately kyphotic position was imposed during exercise no hemolysis occurred when the same or greater amounts of work were performed than necessary to produce a frank attack of hemoglobinuria in the normal walking position
- (4) Local hemoglobinemia was not produced when exercise of the hand was performed in the presence of venous stasis imposed by a tourniquet on the arm
- (5) Hyperventilation for 20 minutes failed to produce hemolysis
- (6) The presence of two precipitating factors were shown in one patient to be required to produce attacks of march hemoglobinuria  
(1) exercise (2) appropriate posture during the exercise

- (7) Hemoglobinuria occurred after a nine minute run in one patient whereas no hemoglobinuria or hemoglobinemia were produced in this patient by a brisk walk of 45 minutes

12 The various theories regarding the etiology of march hemoglobinuria are critically reviewed in the light of the present knowledge of this condition

13 Our studies together with those of others (50) demonstrate that "physiological" hemoglobinemia and hemoglobinuria occur in healthy individuals after marches and runs, provided the exertion is extremely intense and of considerable duration. The same mechanism of intravascular hemolysis apparently operates in patients with march hemoglobinuria who develop attacks on short walks or runs, but the hemolysis occurs following lesser exertion due to some as yet undefined mechanical or postural abnormality. Our experience further indicates that march hemoglobinuria occurs more commonly than the infrequency of its diagnosis suggests. March hemoglobinuria will, perhaps, be observed more frequently than hitherto because of the large number of young men who are now engaged in the strenuous exertion of military training, and who are under close medical supervision. The importance of differentiating this relatively benign condition from more serious conditions leading to the passage of a red urine is apparent.

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# THE ETIOLOGY AND THE CAUSATIVE MECHANISM OF ARTERIOSCLEROSIS AND ATHEROMATOSIS

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The etiology and the causative mechanism of chronic degenerative vascular diseases, i e , atheromatosis and arteriosclerosis, have remained to a large extent controversial subjects. No agreement has been reached concerning the respective roles played in the production of these lesions, on the one hand by physiological senescing processes, possibly conditioned in their time of onset, in their rate of progress, and in their organic distribution by constitutional or hereditary factors, and on the other hand by pathological disturbances of endogenous or exogenous origin and of acquired nature. The situation existing in this respect is complicated by the fact that these vascular manifestations exhibit a remarkable diversity in their anatomical structure, as evidenced by the various names used, such as arteriosclerosis, atheromatosis, atherosclerosis, Monckeberg's media necrosis and calcification, etc , indicating that several fundamentally different causal factors may be reflected by these morphological varieties. The same conclusion is suggested by the observation that there occurs a considerable disparity in the organic distribution and in the time of appearance of these lesions in the different organs. None of the numerous theories so far advanced concerning the etiology of degenerative vascular disease supplies a satisfactory explanation of the multitude and variety of phenomena, or provides an acceptable common denominator of the primary causal dynamics operating in their production.

The general confusion and uncertainty growing out of the controversial claims made and resulting from the lack of reliable and adequate information has interfered seriously with the development and institution of rational and effective preventive as well as therapeutic measures suitable for the control of these vascular disorders. The





ing of the binding substance of the elastic membranes of the media, associated with an infiltration of the interstices of its inner third by a hyaline substance and with a fibrosing degeneration of its muscular elements. Chemically these lesions are said to be related to an aging of the colloids which undergo dehydration, and to an increasing affinity of the vascular tissues thus changed and made denser to certain metabolic waste products such as cholesterol and calcium salts. As these substances possess normally a limited degree of solubility, they precipitate readily when even minor changes in the physico-chemical status of their medium occur. It is argued by the proponents of the senescence theory of arteriosclerosis that these substances which enter the vascular walls by diffusion from the blood are precipitated and accumulated most markedly in close proximity to the arterial lumen, thereby blocking increasingly the filtering surface of the vascular wall to the entrance of nutritive substances essential to the vital activities of its cellular components. As the result of the ensuing impairment of the nutritive conditions of the inner parts of the vascular wall there develop degenerative necrobiotic changes in the affected regions accompanied by reactive proliferations of the subintimal connective tissue and by accumulations of lipophagocytic cells which ultimately form atheromas. It is claimed moreover that the intimal thickenings represent in part attempts toward a reestablishment of the original width of the vascular lumina because, with the progressive degeneration of the contractile elements, the vascular walls lose their elasticity and the lumina become distended.

Arteriosclerosis and atheromatosis are according to this conception (Burger and Schlomka, Liesegang), mainly and primarily the result of a physiological aging of the vascular colloids and are not occasioned by any disturbances of the calcium or cholesterol metabolism, i.e. by substances entering the vascular walls from the outside. Only a precocious appearance of the lipoidal and calcified deposits in the walls of arteries is considered as a sign of a disease.

There exists indeed a juvenile type of arteriosclerosis and atheromatosis which occurs in coexistence with several disease conditions of diverse nature such as diabetes mellitus, nephrosis, xanthomatosis, myxedema and similar hypothyroidotic disorders, adenomas of the adrenal cortex and adrenal medulla and in the special form of sclerosis

urgency for effecting a change in this situation is indicated by the fact that degenerative vascular diseases contribute an appreciable percentage to the annual death rate, that during recent decades a remarkable rise of the United States old-age population has occurred, and that, during the same period, a constantly growing exposure of the general population to exogenous agents possessing vasculo-toxic properties (lead, arsenic, nitrites, carbon monoxide, atmospheric oxygen deficiency, nicotine etc) has taken place for occupational, habitual or environmental reasons

Experiments conducted by the author during recent years and published in part elsewhere yielded evidence suggesting that an interference with the oxygenation and nutrition of the vascular walls is responsible for the various degenerative and proliferative vascular changes characterizing arteriosclerotic lesions, and represents the fundamental causal mechanism regardless of the nature of the etiological agent and of the different morphological and distributory aspects displayed. In view of the considerable medical and social importance of this problem the following analysis of the available clinical, pathological and experimental data in the light of this conception, is offered in the hope that it may prove of value for a more intelligent understanding of the etiology, the causal dynamics, and the preventive and therapeutic control of the degenerative vascular diseases

#### ETIOLOGICAL ASPECTS

A great number of endogenous and exogenous factors of physical and chemical nature have been implicated in the development of these disorders becoming manifest in general during the advanced periods of life. The evidence on which these claims are based is partly factual, partly circumstantial, and partly conjectural. Depending upon their nature and upon the effects produced by them, the various factors of alleged causal significance may be divided into five groups

##### *1 Physiological Senescing Processes*

The physiological senile changes of the arterial walls begin, according to Aschoff, during the fifth decade and are characterized morphologically by a fibrotic thickening of the intima and by a loosen-

found on that occasion that the haired rats which have a considerably longer average life span than the hairless litter mates and thus presumably pass through a slower aging cycle (555 days and 365 days respectively) displayed a much more marked and widespread degenerative and calcifying arterial disease affecting the aorta and the arteries of the heart lung kidney pancreas suprarenal epididymis and testis than that observed in the hairless variety. This experimental evidence indicates that the factors controlling senescence and longevity are not identical with those eliciting arteriosclerotic manifestations and that exogenous influences may play an important role in determining the onset and development of these conditions.

## *2 Physiological and Pathological Mechanical Trauma*

Mechanical trauma to the structures of the vascular walls by physiological or pathological dynamic factors is incriminated by many investigators (Aschoff, Allbutt, Duguid, Harrison, Leary, Adami, Kraika, Menne, Beaman and Labby) as a principal or important contributory causal factor in the development of chronic degenerative arterial disease. It is claimed that a continued mechanical strain affecting especially the sites of vascular fixation (bifurcations) and consisting of tension vibration shearing between intima and media etc. cause a loosening of the connective tissue ground substance or a separation of the intima from the media and favor thereby the imbibition of these areas by the lipid-containing plasma as well as the development of a reactive intimal proliferation. Some investigators contend that the localization of these lesions depends upon mechanical factors of vascular dynamics interfering with the nutrition of restricted areas of the vascular wall and favoring thereby the infiltration of cholesterol through the 'stomata' of the endothelial lining into the subintimal tissue (Leary). Intimal herniation resulting from a stretching of the fenestrae of the elastic membrane by a physiological or pathological intravascular pressure elicits an irritational intimal proliferation and thus represents the general cause of arteriosclerosis and atheromatosis in the opinion of Kraika.

A critical analysis of these conceptions from a more comprehensive viewpoint shows readily that the various calculations and arguments advanced in support of a mechanical traumatic genesis of chronic

of the pulmonary artery, increased hydrostatic pressure in the pulmonary artery as the result of congenital malformations of the heart (open foramen ovale, mitral lesions, etc) Inasmuch as the arterial lesions observed in the young under such circumstances do not differ in any essential respect from those found during a more advanced period of life under similar associated disease conditions or, usually, without such complications, it becomes obvious that normal senescing processes cannot play any important part in their production This conclusion is supported by additional evidence Apart from the fact that the arteriosclerotic changes affect in general only restricted areas of a particular vessel and do not represent a diffuse alteration, these lesions exhibit marked variations in their distribution upon the arteries of the different organs and in their time of onset in the vascular tree of the various tissues Thus, highly sclerotic arteries of the extremities are often not accompanied by changes of similar type and intensity in the arteries of the internal organs Whereas coronary sclerosis occurs frequently in relatively young individuals, arteriosclerotic changes of the cerebral vessels are not found, as a rule, before the senile period of life is reached While these observations may be reconciled with the senescence theory by assuming that the arteries of different parts of the body undergo aging changes at various times and rates, it is more likely that other factors, not connected with physiological senescence, are operative in bringing about the degenerative arterial changes

This conclusion is supported by some experimental evidence obtained from studies on the nature of factors controlling longevity and senescence (McCay) This investigator found that rats, raised from an early period of life on moderately restricted diets with a consequent stunting of growth showed, on the one hand, a general and marked prolongation of their average life span and thus a delay and slowing of the physiological aging processes in comparison with normally and adequately fed rats, but they developed, on the other hand, a precocious and extensive calcifying type of arteriosclerosis of the aorta and coronary and renal arteries Observations of similar nature and significance were recently made by Hueper during a study of the organs of hairless rats and their haired litter mates which had been exposed over a prolonged period to an intense ultraviolet irradiation It was

may be involved in creating conditions fundamentally important for the development of vascular lesions, assuming ultimately the character of arteriosclerosis. The possibility of such a relationship for certain organic types of arteriosclerosis and arteriolosclerosis is suggested by the fact that allergic vascular reactions are characterized by an increased permeability and spasticity of the arteriolar walls, by the precipitation of allergic immune bodies on the endothelial lining by the reactive proliferation of endothelial cells and by the appearance of degenerative changes in the media of the reacting vessels. It is conceivable that degenerative arterial disease may be the end-result of repeated allergic reactions causing an impairment of the nutrition of the vascular walls by medial spasm in connection with the formation of films covering the intima and composed of allergen-immune body complexes.

The results of experimental studies (unpublished) conducted by the author lend support to this conception. Dogs which had been injected five times per week with 10 cc of a 1 per cent amino-antipyrine-azo-protein (egg albumin) solution into the jugular vein for a period of approximately six weeks (total of 230 cc of the sensitizing agent), showed at autopsy small and scarred kidneys and at microscopic study fibrous and hyaline thickenings of the intima of large arteries, foam cellular infiltrations of the subintimal spaces of the aorta, hyaline scars in the aortic media, and hyalinization of the thickened media of the renal arteries. It is of significance that similar degenerative and necrotizing lesions in the aorta and arteries were observed by Holman in dogs which had been injected subcutaneously with uranium nitrate and intravenously daily with canine plasma in amounts of 100 cc (a total of 1 880 to 2 655 cc). Holman considered the possibility that the arterial lesions were the result of an allergic reaction elicited by a conjugated uranium protein.

#### *4 Physicochemical Disturbances of the Blood of Endocrine, Vitaminc or Nutritive Origin*

Certain disturbances of endocrine, vitaminic or nutritive origin causing more or less severe abnormalities in the composition of the blood and thereby in the physicochemical environment of the vascular

arterial disease fall far short of providing a plausible explanation for the existence of the different morphological forms, for the variations in their organic distribution and in their time of onset as well as for the absence of a progressive course in the case of the lipoidal infiltrations occurring in the aortic wall of infants. None of the numerous attempts made to reproduce arteriosclerotic lesions experimentally in animals, either by causing a direct traumatization of the vascular walls from the outside or from the inside of the vessels, or by producing an overdistension of the arterial lumina by mechanical means in an effort to bring about splits and tears in the intima and elastic membranes, resulted in the development of changes identical with or even similar to those characterizing human arteriosclerosis (Amitschkow). Mechanical trauma of physiological or pathological nature seems to play, if any, merely a secondary and minor role in the development of degenerative arterial disease. The allegations made in this respect neglect to take proper consideration of the fact that conditions accompanied by an abnormal mechanical strain to the vascular walls, such as overdistension or overcontraction caused by fluctuations in vascular tonicity or in hydrostatic pressure, exert also a definite and appreciable influence upon the blood circulation of the vasa vasorum and thereby upon the nutrition and permeability of the vascular walls (Moon).

### *3 Infectious and Bacteriotoxic Agents*

The infectious genesis of arteriosclerosis championed originally by Virchow and supported later in a modified form by Klotz, Saltykow, and others has at present only a few proponents. While Virchow at one time claimed that arteriosclerotic lesions represent reactions to bacterial infections of the vascular walls, it was subsequently assumed that bacteriotoxins present in the blood injure the intima and prepare it for the subsequent atheromatous changes by increasing its permeability to cholesterol and fats contained in the plasma. However, MacCallum concluded from an analysis of the available clinical, pathological and experimental evidence that there is little support in favor for the idea that acute or chronic infections play a great part in the pathogenesis of arteriosclerosis and atheromatosis.

It is uncertain, however, whether functional or anatomical allergic reactions to bacterial or, for that matter to other chemical allergens

with the Monckeberg's media calcification, from which it is distinguished, however, by its organic distribution

A great deal of uncertainty prevails regarding the causative mechanisms operating in the production of the calcifications and associated vascular lesions. While Wells, Ham and Lewis, Dietrich, and others favor the view that the arterial calcifications are of metastatic character, i.e. that they represent localized precipitations of calcium salts out of a supersaturated solution into a previously vitally intact tissue and involve sites predisposed to this chemical reaction by local conditions such as alkalinity, stagnation of tissue fluids, etc., other investigators contend that they are typical examples of the tendency of devitalized tissue and of homogenous colloidal structures to absorb substances of low solubility with which the blood is saturated or oversaturated (Simonnet and Tanret)

The following observations support the validity of the last mentioned conception. Shohl, Goldblatt and Brown observed in rats kept on a calcium deficient diet and exposed to toxic doses of roosterol, as severe degenerative and necrotizing arterial lesions as those found in a control group fed a normal diet, while the vascular calcifications in the calcium deficient series were not only less severe, but also delayed in appearance in comparison to the control animals. Similarly, Schmidtmann found that rabbits placed on a prolonged treatment of relatively small doses of vitamin D showed at the time of the cessation of treatment only very mild swellings and cellular infiltrations of the media while animals kept alive thereafter died suddenly some time later following an interval of apparently good health, and displayed severe calcifications of the media, indicating thereby that degenerative changes precede the calcifying processes. Finally, the frequency and regularity with which calcifying media necroses can be produced experimentally by various vasculo-toxic agents (adrenalin, digitalis glycosides, ammonium hydroxide, methyl cellulose) which do not elicit a hypercalcemia, provide sufficient evidence supporting the claim that the existence of a hypercalcemia merely hastens the onset and accentuates the intensity of the arterial calcifications by facilitating the formation of calcium soaps with the lipids present in the alkaline necrotic tissue. It is for this reason that the hypervitaminic media calcinosis can be elicited most readily in animals possessing normally

walls have been charged with the causation of degenerative arterial disease. However, the exact role and significance which these disorders play in the causation and in the causative mechanism of such lesions is still controversial in many respects.

*a Calcium* Disturbances of the calcium metabolism characterized by an elevated blood calcium level have been implicated in the production of the calcifying types of arteriosclerosis. However, the absence of a hypercalcemia in the great majority of individuals showing media calcifications of the arteries of the extremities or calcified atheromatous plaques militates against the actual existence of such interrelations.

It is, on the other hand, a well established fact that the hypercalcemia, occasionally observed in individuals suffering from hyperparathyroidism caused by an adenoma of this gland, may be accompanied by calcified and degenerative arterial lesions (Shelling, Asher and Jackson, Johnson). Similar arterial and arteriolar changes were reported to be present in dogs and rats following the administration of excessive doses of parathyroid hormone (Hueper, Learner, McJunkin, Tweedy and Breuhaus). Whereas the experimental lesions involve mainly the media and elastic membranes of the cardiac and renal vessels, those found in man under such conditions are of a generalized type and affect the media as well as the intima.

A similar, but usually much more extensive arterio-calcinosis involving the medial coats of elastic and muscular arteries (aorta, carotid, coronary, renal, pulmonary and, exceptionally, cerebral arteries) has been shown to follow the introduction of toxic amounts of vitamin D into rabbits, cats, dogs, and rats (Kreitmar and Hintzelmann, Schmidtman, Hueper, Dietrich, Handovsky, Ham and Lewis, Ham and Portuondo, Holtz and vonBrand, Shohl, Goldblatt and Brown, and many others) as well as the prolonged exposure to excessive doses of ultraviolet radiation in rats (Hueper). The development of degenerations in the media consisting of muscular hyalinization and elastic fragmentation is followed by a calcification of these foci and by intimal proliferations in close proximity to the calcified areas. The arterio-calcinosis resulting from hypervitaminosis D and by poisoning with parathyroid hormone differs morphologically from the ordinary atheromatous calcifications, but possesses a certain degree of similarity.



fore ensue not so much as the direct result of a derangement of the mineral metabolism as from functional disturbances of the arterial tonus and of the circulation. This conclusion receives support from the fact that similar cardiovascular dynamic conditions prevailing in overdigitalized animals are evidently responsible for the degenerative lesions observed in the myocardial arteries in the myocardium in the aorta and in the renal arteries (Fischer-Wasels, Klotz, Morelli, Hueper and Ichniowsky).

*b Cholesterol* Hypercholesterolemia of endocrine or nutritional genesis particularly when associated with lipemia, has often been implicated as a factor directly or indirectly involved in the production of atheromatosis (Anitschkow, Tannenberg, Monckeberg, Chalutow, Joslin, Warren, Leary, Page and Bernhard, Leary and Weiss and many others). This contention is based upon several observations: 1. Atheromatous lesions are characterized by the accumulation of lipoids and lipids either contained within foam-cells of endothelial or histiocytic origin or occurring free as extracellular imbibition in the subintimal or medial tissues, 2. diabetes mellitus, myxedema and Hand-Schüller-Christian syndrome are distinguished by a more or less marked hypercholesterolemia as well as by precocious and extensive atheromatous changes, 3. the prolonged oral administration of cholesterol to rabbits results in the development of hypercholesterolemia followed by the appearance of localized or diffuse atheromatous lesions in the arterial tree. While some investigators concluded from this evidence that atheromatosis is primarily the result of a disturbance of the cholesterol metabolism (Anitschkow, Leary), others ascribed to this disorder only a subordinate role (Tannenberg, Duff, Harrison, Landé and Sperry, and others).

Various arguments have been advanced against the significance of hypercholesterolemia in the genesis of atheromatosis: 1. While a hypercholesterolemia is found in an appreciable percentage of individuals with atheromatosis (Poindexter and Bruger and others), this is not a constant finding (Landé and Sperry, Weinhouse and Hirsch, Weinstein and Weiss, and others), 2. the cholesterol present in atheromas does not originate for the most part from the plasma which is taken up by endothelial phagocytosis or seeps through the intimal lining but it is released as the result of phagocytosis from disintegrating

a high blood calcium level (herbivores) and that its development is accelerated and aggravated by the simultaneous administration of parathyroid hormone (Handovsky and Goormaghtigh)

The apparent influence of additional metabolic factors upon the production of a hypervitaminic arteriocalcinosis is evidenced by the observation that the media sclerosis of the aorta elicited by viosterol medication is more severe in thyroidectomized rabbits than in normal ones, as the hypercholesterolemia appearing in rabbits during the course of a hypervitaminosis D is accentuated in thyroidectomized rabbits. This aggravation is due to the fact that thyroidectomy causes also an increase in the cholesterol level of the blood. Conversely, the administration of thyroid substance or of potassium iodide to rabbits treated with vitamin D impedes or prevents the production of a media calcinosis (Handovsky and Goormaghtigh, Simonnet and Tanret). The relationship between and the synergistic action of hypercalcemia and hypercholesterolemia apparent from these observations is illustrated further by the fact that the combined administration of vitamin D and cholesterol to rabbits intensifies the calcification of the resulting atheromas (Leary and Weiss). Such observations evidently furnished the basis for Handovsky's claim that the hypercholesterolemic condition deserves the main emphasis in regard to the genesis of the hypervitaminic arterial lesions. However, Selye pointed out that rats treated with excessive doses of vitamin D and having extensive sclerotic and calcifying arterial lesions did not show any cellular lipoidal deposits in these reactions, such as those seen after the administration of cholesterol or adrenalin.

It is remarkable that little consideration has been given in the various attempts to account for the arteriotoxic action of hypervitaminosis D or parathyroid hormone poisoning to the fact that these conditions are accompanied by serious disturbances of the cardiovascular tonus (increased vascular tonus, elevated blood pressure, slowed cardiac rhythm, and, ultimately, failing circulation) (Appelrot, Handovsky and Goormaghtigh, Handovsky). These effects, in addition to a reduction of the cellular permeability through the increased calcium content of the tissue fluids, may interfere appreciably with the nutrition of the arterial walls. The degenerative vascular lesions seen in parathyroid hormone poisoning and in hypervitaminosis D may there-

blood cholesterol level have no etiological relation to atheromatosis. Inasmuch as cholesterol is chemically a relatively inert substance, it is not readily mobilized from intracellular or extracellular vascular deposits. Hypercholesterolemia, for this reason, may be not of persistent but of transitory character without losing any of its causal significance. This has been definitely shown to be a fact in experiments with rabbits which were subjected to treatment with thyroid substance or iodine preparations after having been exposed previously to oral administrations of cholesterol for a sufficiently long time to insure the production of atheromas, as there was no evidence in the animals thus treated of a resorption of the cholesterol deposited in the atheromas formed (Meeker, Kesten and Jobling). On the other hand, it has been demonstrated repeatedly and conclusively that the treatment of rabbits with thyroid substance or iodine preparations simultaneously with the oral administration of cholesterol prevents or lessens the development of hypercholesterolemia as well as of atheromatosis (Friedland, Turner and Khayat, Murata and Kataoka, Liebig, Seel and Creuzberg, Strauss, Page and Bernhard). In this connection it is noteworthy that the protective action exerted by potassium iodide in experimental cholesterol atheromatosis in rabbits is abolished after thyroidectomy (Turner and Khayat). Similarly, thyroidectomized animals (goats, sheep) develop in addition to hypercholesterolemia a precocious, calcifying atheromatosis (Falta, vonEiselsberg, Pick and Pineles), while a dietary cholesterol atheromatosis appears more rapidly in thyroidectomized rabbits than in normal ones (Shapiro). Mention may be made of the fact that individuals with hyperthyroidism display not only a lowered blood cholesterol level, but are also rarely affected by atheromatosis (Schally, Rosenthal, and others). Inasmuch as Leary and Weiss demonstrated that cholesterol atheromas of rabbits persist for many months after the cessation of the ingestion of cholesterol, while undergoing at the same time fibrosing and calcifying changes, it is obvious from the evidence presented that transitory hypercholesterolemic episodes of endocrine or nutritive origin and of adequate strength and duration may be instrumental in the causation of atheromatosis, and that a persistent hypercholesterolemia is not essential for the establishment of etiological interrelations between these two conditions (Monckeberg).

It is of importance in this connection that the development of an

erythrocytes present in subintimal hemorrhages from capillary vasa vasorum (Winternitz),<sup>3</sup> as hypercholesterolemia is a general condition of the blood, it cannot by itself cause atheromatous lesions, as these are localized and not diffuse changes of the arterial walls,<sup>4</sup> the experimental cholesterol atheromatosis following oral administration of excessive amounts of cholesterol can be elicited successfully only in rabbits,<sup>1 e</sup> in herbivorous animals, for which such a diet is not only highly unbalanced but also unnatural, and thus may cause a deviation of the normal metabolism, especially as the rabbit does not possess a metabolic mechanism adequate for rapid elimination or degradation of appreciable amounts of cholesterol, which are therefore retained in the body over prolonged periods,<sup>5</sup> attempts to produce atheromatosis in carnivorous or omnivorous animals by the same experimental procedure have failed, presumably because of the inability to obtain by this method a persistent hypercholesterolemia in animals of species which normally can dispose rapidly of considerable amounts of cholesterol through the various metabolic processes,<sup>6</sup> in the atheromatous cholesterolized rabbit, cholesterol deposits are present not only in the walls of the arteries, but also in numerous other organs (liver, spleen, lymph nodes, etc.), while such reactions are in human atheromatosis not the rule, but rare exceptions, being found only in xanthomatosis, Hand-Schuller-Christian disease, etc.,<sup>7</sup> an additional important difference between human atheromatosis and experimental cholesterol atheromatosis in rabbits, reducing the alleged causal significance of this condition, is seen in the fact that the atheromatous changes affect in man mainly the abdominal portion of the aorta, whereas they involve in the rabbit the ascending part of this vessel.

While some investigators have drawn from this evidence and from these arguments the conclusion that a disturbance of the cholesterol metabolism is not an essential prerequisite to atheromatosis, or that hypercholesterolemia, when coexisting with atheromatosis, is merely coincidental or is an effect of atheromatosis (Duff), there exists a considerable amount of data attesting the direct and considerable etiological importance of plasma cholesterol in the genesis of these arterial changes, and refuting the validity of the arguments cited against such a relationship. The absence of a hypercholesterolemia in a certain percentage of individuals with atheromatosis cannot be

ference with the circulation of the tissue juices exists and where therefore an excess of carbon dioxide prevails Mönckeberg similarly incriminated local nutritive disturbances in the vascular wall as the cause of the phagocytosis and imbibition of cholesterol Wells on the other hand considered the causative mechanism operative in the production of the experimental dietary cholesterol atheromatosis to be a simple precipitation phenomenon He argued that cholesterol being a poorly soluble substance and present in the blood in a supersaturated state is deposited in the vascular wall as a sort of metastatic cholesterolemia forming thus a counter-part to the arterial metastatic calcification observed as the result of hypercalcemia, according to the same investigator It is held that the simultaneous presence of a lipemia favors the development of the atheromatous responses This factor is emphasized especially by Hirsch who stated that atheromatous reactions result only when the cholesterol is present in the blood in a state of colloidal dispersion since the intravenous introduction of unemulsified cholesterol causes the appearance of foreign body reactions in the pulmonary vessels

Inasmuch as young cells exhibit a tendency to accumulate lipoids Tannenbergs concluded that a proliferation of intimal cells precedes the deposition of lipoids and thus the formation of atheromas This conception contrasts with that held by Anitschkow and others who maintained that degenerating or necrotic areas produced by various means in the vascular walls display a special affinity for lipoids However recent experiments of Jobling and Meeker who combined the cholesterol treatment of rabbits with various other procedures (intravenous injection of streptococcus toxin peptone uric acid etc or feeding of ammonium chloride anaphylactic shock artificial fever) designed to accelerate the development of atheromatosis by producing an additional injury in the vascular walls gave negative results suggesting that the formation of cholesterol atheromas is not dependent upon the previous presence of tissue necroses

Tannenberg proposed that the region in the vascular wall where the nutritive current entering by diffusion from the vascular lumen meets with the current originating from the vasa vasorum represents possibly a site of predilection for the precipitation of substances such as lipoids as in this area a certain degree of stagnation prevails Inasmuch as

experimental nutritive hypercholesterolemia results not only from the direct oral introduction of excessive amounts of cholesterol, but also from a diet of high protein content, lacking appreciable quantities of cholesterol (Newburgh and Clarkson, Meeker and Kesten). These observations indicate that unnatural diets or nutritive imbalances of various types may be involved in the production of metabolic disturbances eliciting an increase of the blood cholesterol level, and underline the causal importance of hypercholesterolemia of a persistent or transitory type in the genesis of atheromatosis.

The study of early human as well as of experimental atheromatous lesions in rabbits leaves no doubt that the main source of the cholesterol found in atheromas is the blood plasma. While it may be conceded that, in rare cases, cholesterol from disintegrating erythrocytes present in intimal or subintimal capillary hemorrhages may contribute to the lipid content of intimal thickenings, it is certain that hemorrhagic episodes of this type are not the primary and main cause of atheromatosis.

The usually localized character of atheromatosis does not militate against the causal role of hypercholesterolemia, as local conditions in the vascular walls such as the distribution of the vasa vasorum or peculiarities of the blood flow in different parts of the vascular tree (bifurcations, static conditions, etc.) may readily account for this phenomenon. No valid objections can be advanced against the value of the experimental cholesterol atheromatosis in rabbits as to the genesis of this condition in man, as the occurrence of the juvenile type of atheromatosis in association with persistent hypercholesterolemia (diabetes mellitus, xanthomatosis, hypothyroidism) demonstrates adequately that the human organism reacts to the same metabolic disturbance in the same fashion as that of the rabbit.

While the evidence presented leaves little doubt concerning the causal importance of cholesterol in the genesis of atheromatosis, there still exists great uncertainty in regard to the causal mechanism through which this substance elicits these vascular reactions. Aschoff assumed that the vascular tissue acquires under certain physiological or pathological conditions related to senescence a special affinity for cholesterol leading to the accumulation of this substance in the intima. Beneke contended that lipid deposits appear where a local inter-

nutritional cholesterosis of rabbits. Additional points of resemblance between cholesterosis and polyvinylolosis are supplied by the following facts. Polyvinyl alcohol just like cholesterol is chemically a relatively inert substance which forms with the plasma finely dispersed emulsions, paralleling the so-called protective qualities of cholesterol based on the high resistance of this substance to enzymatic degradation and on its impermeability to many agents, polyvinyl alcohol displays a comparatively marked chemical stability, refractoriness to the normal tissue enzymes, and an impermeability to fats, oils, greases and gases. Because of its macromolecularity and the lack of adequate means of degradation, polyvinyl alcohol is retained over prolonged periods in the blood and tends to coat the inside of vessels and the surface of the erythrocytes with a film. These films are either the result of a coalescence of fine droplets of polyvinyl alcohol or they are the products of a precipitation of this substance in the interface between plasma and intima, as the solubility of polyvinyl alcohol depends upon salt concentration and other physicochemical factors.

The formal genesis of polyvinyl alcohol atheromatosis also follows closely the pattern displayed by the cholesterol variety. The endothelium of the elastic vessels takes up the foreign matter from the blood and is transformed thereby into large swollen foam-cells. Following a reactive proliferation of the damaged endothelial cells resulting in the formation of more or less thick cushions of foam-cells, and subsequent to a penetration of the polyvinyl alcohol into the media, foam-cellular endothelial histiocytes invade the inner part of the media. The accumulation of polyvinyl alcohol in the endothelial histiocytes and in the interstices of the media is followed by the appearance of small numbers of fatty granules in the endothelial foam-cells and in the muscle cells of the media and in the polyvinyl alcohol infiltrating these parts of the vascular wall. While the fatty substances found in the endothelial lining may be derived from the blood, those present in the media are apparently the result of phagocytosis and cellular decay. The affected usually markedly loosened parts of the media reveal muscular degeneration and hyalinization as well as disintegration of the elastic fibrils. In moderately polyvinylized animals these changes are restricted to the inner third of the vascular wall. However in severely polyvinylized animals there occur similar focal foam-cellular

this zone of stagnating tissue fluids should be located somewhere in the inner third of the media, and in view of the fact that the earliest atheromatous changes are observed in the intima or directly beneath it, while the media remains intact during this stage, it is evident that this theory cannot be reconciled with the facts. Similar objections may be raised against the claim made by Schmidtman, that the hypertension accompanying the hypercholesterolemia of rabbits is responsible for the atheromatous changes observed, as it is well known that hypercholesterolemia and atheromatosis coexist in man not infrequently in the absence of an increased blood pressure. Hypertension represents therefore under such conditions merely a possible contributory factor, but not an essential one.

It is obvious that none of the existing theories concerning the genesis of atheromatosis in the presence of a pathological and persistent hypercholesterolemia or in its relation to physiological fluctuations in the cholesterol content of the plasma offers any reliable or plausible information concerning the primary dynamics of this process.

*c Polyvinyl Alcohol* The recent investigations on the production of polyvinyl alcohol atheromatosis in animals by Hueper are for this reason of particular interest as they throw some new and additional light upon the causative mechanism operative in the production of atheromatosis in general. The intravenous, intraperitoneal or subcutaneous injection of an aqueous colloidal solution of polyvinyl alcohol into dogs, rabbits and rats results in the development of vascular and organic lesions containing polyvinyl alcohol. Extensive atheromatous changes occur in the elastic and muscular arteries and arterioles of various organs and foreign body giant cell granulomas develop in the pulmonary vessels as the result of the phagocytosis, imbibition and deposition of polyvinyl alcohol in endothelial and histiocytic foam-cells and in the interstices and muscle cells of the media. These vascular reactions are morphological equivalents of the cholesterol atheromatosis. The immobilization of appreciable amounts of polyvinyl alcohol in the reticulum and reticulo-endothelial cells of the spleen, lymph-nodes, liver, adrenal subcutaneous tissue, etc., is characterized by the appearance of larger and smaller groups and nodules of foam-cells containing polyvinyl alcohol, which again are similar to those found in xanthomatosis, lipoidoses, diabetes mellitus and in the



scattered media calcifications in the aorta partially calcified atheromatous changes in the aorta, pancreatic artery and, most extensively, in the left auricle. The large, plate-like calcium incrustations of the thickened foam-cellular endocardium affect mainly the necrotic portions and are located in that part of the heart where the blood has a lowered carbon dioxide tension favoring the precipitation of calcium salts (Wells).

While these findings are of distinct importance from the standpoint of pathology, the information which they yield in regard to the causal genesis of atheromatosis and arteriosclerosis is of even greater significance. The data presented permit the conclusion that polyvinyl alcohol present in the blood as a finely dispersed emulsion and coating the vascular endothelial lining of blood vessels, interferes with a normal and adequate exchange of the various gaseous and liquid nutritive substances and waste metabolites between the blood and the inner third of the vascular walls. The resulting cellular injury is intensified when the polyvinyl alcohol is taken up by the endothelial cells and infiltrates the vascular wall causing a further clogging of the normal filtration membrane. The reactive proliferation of the endothelial cells and their foam-cellular transformation produces atheromatous lesions. The physicochemical qualities of polyvinyl alcohol films toward fatty substances and the absence of any appreciable amounts of fat-stainable material in these lesions as well as of any hypercholesterolemia, exclude any significant role of lipids in the development of these vascular changes.

The validity of this conception is supported by the results of experiments by Martin and Hueper designed to demonstrate the effect of film formation by polyvinyl alcohol upon the oxygenation speed of erythrocytes of polyvinylized dogs. While the methods used for this purpose are of purely relative character, the results obtained supply adequate information concerning the condition investigated. A blood sample (5 cc) is evacuated to 20 mm of mercury for five minutes and is then exposed to oxygen of the atmosphere for five seconds. A manometric oxygen determination is immediately carried out thereafter. Table 1 presents the results obtained with this procedure on blood tested before the intravenous injection of 130 cc of a 5 per cent polyvinyl alcohol solution and again 24 hours later.

accumulations throughout the entire vascular wall, especially in the perivascular region of the vasa vasorum, which show under such conditions also a foam-cellular swelling of their endothelium. The media of the organic muscular arteries often exhibits in addition to similar endothelial changes a marked vacuolization of the muscle cells, the vacuoles being filled with globules of polyvinyl alcohol. It may be mentioned that polyvinyl alcohol atheromatosis not infrequently affects the aortic leaflets by a direct extension of the foam-cellular endothelial proliferation from the basal parts of the aorta upon the valves. Occasionally, a more or less thick coating of foam-cells covers the inside of the left auricle and permeates its entire wall. Necrosis, hemorrhages and newly formed capillaries are found in some of the more abundant foam-cellular proliferations.

Polyvinyl alcohol atheromatosis resembles thus closely in developmental as well as morphological respects the corresponding atheromatous changes found in the larger vessels and the lipid degeneration of the media of the arterioles present in human atheromatosis. Its similarity with the experimental cholesterol atheromatosis is equally close not only as to development and morphology, but also in regard to local distribution as the ascending portion of the aorta of the polyvinylized animals exhibits more marked atheromatous lesions than the abdominal part. On the other hand, polyvinyl alcohol atheromatosis does not display the species-specific limitation possessed by experimental cholesterol atheromatosis. This distinction of the polyvinyl alcohol atheromatosis is evidently due to the fact that no species is provided with a metabolic mechanism capable of disintegrating this synthetic, foreign, macromolecular material.

In contrast to cholesterol atheromatosis in man, the polyvinyl alcohol variety does not show any tendency toward calcification in lesions up to three months old. However, a calcifying type of polyvinyl alcohol atheromatosis can be elicited by combining the parenteral administration of polyvinyl alcohol with an oral ingestion of excessive amounts of vitamin D. Puppies two to three months old receiving 25 cc. of a 5 per cent polyvinyl alcohol solution intravenously twice a week and 50 000 to 250 000 units of vitamin D daily by mouth until a total of 8 to 10 million units is given during a period of 55 days, show in addition to extensive polyvinyl alcohol atheromatous lesions and

*d Methyl Cellulose* Observations made during the course of experiments on the toxicopathological effects of repeated parenteral injections of aqueous solutions of a highly viscous type of methyl cellulose into rabbits and dogs lend additional valuable support to the conception of the causal dynamics of atheromatosis developed from the study of cholesterol atheromatosis and polyvinyl alcohol atheromatosis. Methyl cellulose is a macromolecular polysaccharide which possesses physicochemical properties similar in many respects to those of polyvinyl alcohol. Its viscous aqueous colloidal solution forms with plasma a relatively stable emulsion. It is precipitated out of its

TABLE 2  
*Oxygenation Speed of Erythrocytes of Cholesterol-fed Rabbits*

RABBIT	CHOLESTEROL mg/100 cc	R.B.C.	Hb	VOL. PER CENT O <sub>2</sub>	O <sub>2</sub> /Hb
1	796	3,450,000	7.6	7.95	1.04
2	770	4,250,000	9.4	10.3	1.10
3	1020	5,050,000	9.4	12.0	1.26
4	1020	6,800,000	12.3	14.6	1.18
5	639	6,110,000	10.2	9.6	0.95
Control a	64	3,910,000	10.0	14.9	1.49
Control b	42	5,200,000	12.5	18.0	1.44
Control c	60	4,190,000	11.3	16.3	1.42

aqueous solution by ammonium sulfate, behaving in this respect like euglobulin. Films of methyl cellulose, which is chemically relatively inert, render surfaces impervious to the penetration of oils and greases of mineral or vegetable origin.

A two per cent solution of this chemical in normal saline was injected intravenously in daily doses of 20 cc into rabbits and in daily amounts of 65 cc into dogs for periods of eight to ten weeks. In addition to extensive organic storage phenomena in the spleen, liver, kidney, lymph nodes, etc., there occurred in numerous large and small arteries localized proliferations of foam-cellular intimal histiocytes producing coating of varying thickness or nodular formations. Older lesions were markedly cellular and had in part a sclerosing character. The media underneath the foam-cellular cushions in the aorta exhibited

It would seem to follow that a coating of the surface of erythrocytes by polyvinyl alcohol interferes with the interchange of gases across the interface. Anoxemia and impairment of the nutrition of the vascular wall by diffusion of vitally essential substances from the blood are thus the primary effects of polyvinylolosis and form the basis of the subsequent phagocytic, proliferative and degenerative changes which ultimately result in the development of atheromas.

The application of this method to the blood of rabbits which had 2 grams of cholesterol in peanut oil added to the daily ration of rabbit chow over a period of 9 to 12 weeks, demonstrates that similar condi-

TABLE 1  
*Oxygenation Speed of Erythrocytes of Polyvinylized Dogs*

	DOG					
	415	417	419	442	443	454
Vol. per cent O <sub>2</sub>						
Control	11 90	13 11	11 42	11 40	9 60	11 20
24 hour	7 40	8 35	6 25	7 90	4 90	4 60
Hemoglobin						
Control	11 8	13 0	12 0	10 3	9 8	9 9
24 hour	10 8	10 1	11 0	8 8	6 9	7 4
Vol per cent O <sub>2</sub> /Hb						
Control	1 01	1 01	0 95	1 10	0 98	1 13
24 hour	0 68	0 82	0 57	0 89	0 71	0 62

tions as to the oxygenation speed of erythrocytes prevail in the lipemic blood of these animals. In a series of five rabbits thus studied, two (nos 1 and 2) had been on the above described diet for 12 weeks and had then been placed on a normal diet for 8 weeks before the tests were made, while in three animals (nos 3, 4 and 5) the special diet was maintained for 8 weeks and the tests were performed immediately afterwards. Table 2 shows the results obtained. The corresponding figures of the blood of three normal rabbits are included as control values.

The results of these investigations suggest strongly that the causal mechanism active in the production of polyvinyl alcohol atheromatosis and of cholesterol atheromatosis is fundamentally identical.

phenomena caused by the same agent (Davis and Klamer) or that hypertension is the result of arteriosclerosis (Montz and Oldt; Scott)

While the frequent coexistence of and the alleged relationship between hypertension and arteriosclerosis has been a subject of intensive study for many years it is only very recently that evidence was advanced indicating that agents which lower the vascular tonus and cause hypotension and a slowing of the blood flow may also exert an arteriosclerotic effect (Hleper)

*a. Hypertensive-Hypertensive Agents.* Vasoconstricting pressor substances are partly of endogenous, partly of exogenous origin. Endogenous agents of this type are produced normally in the suprarenal gland by both the medulla (adrenalin-epinephrin) and the cortex and in the posterior portion of the pituitary (pituitrin-pitressin). A pressor principle is generated by the normal kidney (renin) and, especially by the ischemic kidney. It may be mentioned that apparently intermediates of melanin which are chemically related to epinephrine are also capable of producing hypertension as melanosarcomas with bilateral metastatic destruction of the suprarenal gland have been found repeatedly in association with marked and persistent elevations of the blood pressure.

The majority of the exogenous hypertensive agents are derived from vegetable matter (ephedrine, ergot, digitals) others are of chemically related nature but of synthetic type (amphetamine, tyramine, etc.) or are metals (lead).

Whereas clinical and experimental evidence attesting a vasculotonic action of most of these substances is available, there exist for a good number of them sufficient factual data indicating their ability to produce arteriosclerotic lesions.

*A. Suprarenal Medulla.* The presence of medullary adenomas (pheochromocytomas) of the suprarenal as well as the repeated and prolonged administration of adrenalin for therapeutic purposes resulting in the production of paroxysmal hypertension have been found to be accompanied in many instances including juveniles by the occurrence of a severe and generalized atheromatosis and medial arteriosclerosis with calcification (Paul, Biedl and Wiesel; Wiesel; Kremer, Hoffmeyer, Nazum and Daton; Raab, Erdheim, Jørgensen, Eisenberg and Walestein and others). Similar medial necroses

often large hyaline necroses which had not infrequently undergone calcification. The media of the smaller muscular arteries was highly vacuolated.

Apart from the fact that these findings support the view that an impairment of the oxygenation and nutrition of the inner parts of the arterial walls, resulting from disturbances of the physicochemical status of the blood, is responsible for the development of certain types of arteriosclerosis and atheromatosis, there remains the question, whether changes in the colloidal equilibrium of the plasma caused by the presence of macromolecular substances of primary or secondary foreign character may play a role in these reactions and may thus represent a more general fundamental etiological principle.

### *5 Agents Affecting the Vascular Tonus and the Circulation of the Blood*

Clinical as well as experimental observations link arteriosclerotic and arterionecrotic lesions with the action of agents affecting the vascular tonus and the circulation of the blood. Inasmuch as such changes, if sufficiently widespread, modify the blood pressure by determining the peripheral resistance to the blood flow, many investigators consider arterial hypertension as the main causal factor of degenerative vascular disease (Monckeberg). However, in evaluating such relations, attention must be given to the fact that an increased blood pressure is not always the result of a pathological functional constriction of the peripheral arterioles, but may result from other causes, such as an increased pumping action of the heart, an elevated blood volume, an increased viscosity of the blood, or a reduced elasticity of the vascular walls. It is probably for these reasons that there are cases on record in which a hypertension was present for several years without being accompanied by arteriosclerosis at autopsy (Hick). On the other hand, it is a well established fact that extensive arteriosclerotic changes may be found in individuals without hypertension. Such observations may be attributable to the absence of a hypertonic causal mechanism in these particular instances, or to the presence of hypertonic influences of such restricted regional type that they were not reflected by an elevation of the general blood pressure (Pal). The apparently contradictory nature of these findings has given rise to the claim that hypertension and arteriosclerosis are merely coincidental

tive changes ensue from a disturbance of the nutrition of the vascular wall due to an impeded circulation in the vasa vasorum and an impaired fluid exchange in the wall of the affected vessels produced by ischemia (Erdheim). The last mentioned view is held by only few investigators especially Lange. The intimal proliferations frequently accompanying more prolonged actions of adrenalin are looked upon in general as compensatory phenomena.

**B Adrenal Cortex and Pituitary** Arteriosclerosis of marked degree and precocious appearance has been observed in individuals with tumors of the suprarenal cortex as well as in persons with a basophilic adenoma of the anterior lobe of the pituitary which is usually associated with a hyperplasia of the adrenal cortex (Fishberg, Mamzer, Moltschanoff and Davydowski, Cushing and others). Both types of tumors are accompanied by a continuous vascular hypertension. It is of importance in this connection that Ferrebee, Ragan, Atchley and Loeb found that large doses of desoxycorticosterone can elicit hypertension in man. This observation is in disagreement with the conception held by Raab who asserted that the vascular hypertonia and arteriosclerosis found in connection with adrenal cortex hyperplasia or neoplasia is due to the action of a cortical lipid-adrenalin complex.

There exists no valid evidence indicating that the posterior pituitary liquid (pituitrin, pitressin) plays a part in the pathogenesis of hypertension and thus of arteriosclerosis (Grollman, Harrison and Williams, Hoyle, Page).

**C Kidney** Clinical observations and experimental evidence show that chronic glomerulonephritis, chronic pyelonephritis, chronic perinephritis and chronic obstruction of the blood flow in the renal artery causing renal ischemia are accompanied by arterial hypertension and arteriosclerosis. While it is known from the experimental work of Goldblatt, Page, Wintermütz and others on renal hypertension that the production of a renal ischemia is followed by an increase in blood pressure and that subsequently widespread arteriosclerotic and arterionecrotic lesions are observed, there is no agreement on the point, whether in human hypertension of renal origin the arterio- and arteriosclerosis of the renal vessels is a primary local degenerative process preceding the development of the hypertension and being responsible for it (Scott) or whether the vascular lesions are the result

have been elicited in the aorta and in the coronary arteries of rabbits by the repeated injection of adrenalin by many investigators (Josué, Thorel, Schultz, Fischer-Wasels, Iwanowsky, Stief and Tokay, and others) The experimental medial degenerations are spotty and circumscribed lesions The muscular debris primarily formed is replaced later by connective tissue or undergoes calcification or liquefaction resulting in cavitation with edematous fluid between the cellular debris There is no leucocytic reaction, but a regeneration of hypertrophied muscle cells may ensue A proliferation of the intima located in proximity to the injured medial area, as well as a deposition of cholesterol into these intimal thickenings, may appear subsequently The thoracic aorta of rabbits is the main site of these lesions, while the abdominal aorta and the pulmonary artery are less extensively involved (Anitschkow) Boveri as well as von Korányi reported that the administration of iodine preparations simultaneously with the introduction of adrenalin prevents the development of adrenalin sclerosis in rabbits

Hyperadrenalism has been implicated for these reasons by some observers (Goldzieher, Paul, Fischer-Wasels, Marchand) as a main factor active in the genesis of human arteriosclerosis, and experimental medial sclerosis caused by adrenalin treatment has been likened to the media calcification of Monckeberg (Lange) However, there exists no reliable evidence indicating the presence of a hyperactive suprarenal gland in the great majority of cases of human arteriosclerosis The absence of an increased adrenalin content of the blood and of a morphologically demonstrable hyperplasia of the suprarenal medulla militates against the existence of a causal relationship between hyperadrenalism and ordinary arteriosclerosis (Monckeberg, Jores, Eisenberg and Wallerstein) while the different local distribution of adrenalin sclerosis and of Monckeberg's media calcification of the arteries of the extremities points to different causal factors for these two conditions

The causative mechanism responsible for the adrenalin media necrosis has been variously explained Some investigators assert that the muscular degenerations are the result of a functional overexertion of the media, caused by the vascular hypertension, others believe that adrenalin exerts a direct toxic effect upon the muscle tissue of the arteries, while a third group of investigators claims that the degenera-



occupational contact with tobacco or nicotine in the form of dust or spray or an environmental exposure to these agents in the form of smoke may not only be etiologically related to the development of a thrombo-angitis obliterans but also to hypertension and arteriosclerotic changes especially of the coronary arteries (Aschoff Hilpert-Strauss Amitschkow Koelsch English Wilkins and Berkson Wright and Moffat. Moyer and Macdock. Weicker and many others). Whereas the clinical and statistical evidence such as occurrence of angina pectoris cardiac palpitation tachycardia or bradycardia hypertension frequency of coronary sclerosis and related cardiovascular manifestations (supporting a vasospastic and subsequently arteriosclerotic action of nicotine) is not entirely conclusive, it may be mentioned that Adler and Hensel by the administration of nicotine to rabbits produced arteriosclerotic lesions similar to those elicited by adrenalin.

Raab proposed that nicotine exerts such an effect by mobilizing adrenalin thereby making adrenalin the directly active agent. This conception receives some support from the observations made by Staemmler in rats subjected to chronic nicotine poisoning. Staemmler found in an appreciable proportion of rats thus treated medullary adenomatous hyperplasias of the adrenal in addition to a sclerosis of various organic arteries resembling that seen in adrenalin poisoning (Schmiedl).

F Digitalis Glycosides While it is asserted that the circulatory changes following the therapeutic administration of digitalis glycosides are secondary to the effects on the cardiac ionus direct vasoconstrictor effects and marked hypertension can be demonstrated when this drug is used in experimental animals (Buckensdorfer and McGugan). It is therefore of significance that Fischer-Wasels Klotz and Morelli observed in rabbits the occurrence of medial necroses and calcifications after the injection of digitalis preparations and that Hueper and Ichonovski reported the presence of edema and hyaline degeneration of the coronary and renal arteries and arterioles in cats similarly treated. It may be noted also that over-digitalization in man may result occasionally in transient blindness such as is seen not infrequently in connection with chronic lead poisoning as the effect of ischemia caused by a transitory spasm of the cerebral arteries.

G Causative Mechanism of Hypertensive Arteriosclerosis Consid-

of a prolonged vasospasm elicited directly or indirectly by a renal pressor principle generated in a diseased kidney or by some extra renal hypertensive factor, making in the latter case the parenchymatous renal changes secondary to the vascular ones, which in turn would represent a partial phenomenon of a more generalized arterial disease. It is obviously often difficult or impossible to reconstruct from clinical or pathological data the correct sequence of events. However, the known facts indicate that renal hypertension may be primary when caused by renal ischemia, as well as secondary when following the parenchymatous changes ensuing from a primary renal arterio- or arteriosclerosis elicited by some extrarenal arteriosclerogenic agent.

It is also uncertain whether the medial necroses characteristic of malignant human nephrosclerosis and found in dogs during the late stage of ischemic renal arteriosclerosis, are caused by the same agent which elicits the sclerotic lesions of benign nephrosclerosis, or whether they are attributable to the action of a special, accessory, necrotizing factor (Winternitz) which is superimposed upon the pressor agent. Whereas a definite decision is not possible at this time, proper consideration should be given to the fact that many arteriosclerogenic agents (adrenalin, vitamin D, parathyroid hormone, nicotine, lead, digitalis glycosides, nitrites, etc.) seem to favor the development of regressive and sclerosing lesions when acting in moderate intensity and over prolonged periods, while causing medial necroses in excessively large doses.

D Lead. Environmental and occupational exposures to lead and its compounds have shown that this metal elicits a spastic reaction in the smooth musculature, including that of the arteries and arterioles of various organs, especially the brain and the kidneys, resulting not only in secondary functional disturbances and parenchymatous changes in these organs, but also in sclerosis and calcifications of the arterial and arteriolar walls. It is noteworthy in this connection that chronic lead poisoning is not consistently associated with hypertension, but that in many instances the blood pressure is either normal or even reduced, illustrating strikingly the fact that more or less locally-restricted arterial hypertonia is not necessarily reflected by an elevation of the general blood pressure.

E Nicotine. Observations made among workers of the tobacco industry as well as among habitual smokers suggest that an excessive

obvious that a lengthening of the systolic phase associated with an exaggerated myocardial contraction creates a state of circulatory stasis in the myocardial vessels resulting in turn in the production of a myocardial anoxemia, which is most pronounced in those parts of the myocardium located near or beyond the end of the blood supply line i.e., the subendocardial and papillary regions where the ischemic necroses and hemorrhages are found. It may be added that very similar myocardial changes occur in connection with adrenal poisoning (Franz, Josué, Fischer-Wasels, Ziegler, Stief and Tokay, Iwanowsky, Fleisher and Loeb, and others)

*b Hypotonic-Hypotensive Agents* Vasodilating depressor substances are either the products of endogenous metabolism, such as histamine, acetylcholine and its derivatives (mecholyl and the like) or they are of exogenous origin, such as inorganic and organic nitrites and nitrates (sodium nitrite, amyl nitrite, nitroglycerin, erythrol tetranitrate ethylene glycol dinitrate mannitol hexanitrate, etc.), methyl xanthines (caffeine, theobromine theophylline, aminophylline), ethyl alcohol barbiturates carbon monoxide, cyanide, atropin, etc. While some of these agents display, when given in moderate doses, a more or less transitory vasopressor effect by acting either simultaneously on the heart (caffeine) or by containing a pressor component (acetylcholine), all of them are vasodepressants when present in excessive amounts and may cause a persistent hypotension when acting over prolonged periods (barbiturates nitrites)

The relative rarity of pathological hypotensive states in comparison to the incidence of hypertensive conditions may account in part for the fact that little attention has been paid heretofore to the possibility that regionary or generalized vascular hypotonia may be involved in the production of arterial degenerative disease. It is, however, a well established observation that an inordinately prolonged and intensive relaxation of the arterial walls with resulting fall in blood pressure and slowing of the blood flow is followed by a proliferation of the intima and by a degeneration of the media with gradual obliteration of the vascular lumens (Ceelen Fischer-Wasels). Moon has pointed out moreover that an undue distension of the vascular wall causes a compression of the vasa vasorum.

Recent clinical pathological and experimental evidence supports

ering the evidence presented concerning the apparent relationship between arterial hypertonia and degenerative vascular disease, it stands to reason that prolonged or frequently recurring excessive contractions of the arterial walls effect a disturbance of the nutritive conditions and the oxygenation of the tissues and thereby elicit regressive changes. The following causative mechanism is active. Inordinate vasoconstrictions result in a reduction of the blood flow of the vasa vasorum as these are compressed by the contracting media causing thereby, especially in the inner portions of the vascular wall, ischemic hypoxemia accompanied by an accumulation of metabolic waste products. There is moreover an increased production of these metabolites because of the extraordinarily marked functional activity of the muscle cells. The ensuing injury to the vascular tissues, especially their sensitive endothelial lining, leads finally to the development of an increased permeability with the subsequent infiltration of constituents of the plasma, thereby preparing the way for secondary degenerative and necrotizing reactions as well as proliferative responses.

The validity of this conception is attested by dynamic conditions present in the heart of animals subjected to lethal poisoning by parathyroid hormone (Hueper), vitamin D, and digitalis glycosides (Lewitzsky, Bauer, Bauer and Fromherz, Bauer and Reindell, Hu, Lieu and Li, Lendle, Korth and Spang, Lindner, Buchner, Weese and Dieckhoff, Schulze, Hueper and Ichniowski), which leads to the production of myocardial as well as arteriolar lesions. In an evaluation of the causative factors responsible for the hemorrhages and myocardial necroses found under these conditions, it is of significance that the topographical relations of the myocardial arteries and arterioles to the surrounding muscular tissue of the heart are approximately the same as those of the vasa vasorum to the muscle tissue of the arterial media. The cardiac effect elicited by excessive doses of the three substances mentioned consists of an extraordinary prolongation and accentuation of the systolic contraction and of an incomplete and shortened diastolic dilatation of the ventricles. Inasmuch as normally the coronary arterial circulation is at a standstill during the peak of the systole because the coronary arterioles are compressed by the bulges of the contracting myocardium (von Anrep, Fock), it is

obvious that a lengthening of the systolic phase associated with an exaggerated myocardial contraction creates a state of circulatory stasis in the myocardial vessels resulting in turn in the production of a myocardial anoxemia, which is most pronounced in those parts of the myocardium located near or beyond the end of the blood supply line i.e., the subendocardial and papillary regions where the ischemic necroses and hemorrhages are found. It may be added that very similar myocardial changes occur in connection with adrenalin poisoning (Franz, Josué, Fischer-Wasels, Ziegler, Stief and Tokay, Iwanowsky, Fleisher and Loeb, and others)

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Recent clinical, pathological and experimental evidence supports

the contention that prolonged or often repeated arterial hypotension is an important etiological factor in the development of arteriosclerosis by interfering with the proper oxygenation and nutrition of the vascular walls

**A Histamine** Histamine which produces, when given in sufficient doses, a marked relaxation and a considerable increase in the permeability of the vascular walls followed by a pronounced drop in blood pressure, elicits in rabbits subjected to small doses over a prolonged period, a swelling and plasmatic infiltration of the walls of the small and medium sized coronary arteries with clumping of the nuclei. The pulmonary arteries are firmly contracted and display a swollen and loosened media and local intimal thickenings (Heinlein, Meessen, Ruhl). In more advanced stages of chronic histamine poisoning, the media of the myocardial coronary arteries is replaced by connective tissue, and the myocardium, especially the papillary muscles, contains numerous necroses and hemorrhages. Meessen as well as Heinlein attributed these changes to the production of a stagnant anoxemia resulting from the circulatory failure. The ensuing endothelial damage and increased vascular permeability to plasma ultimately leads to the development of sclerotic lesions.

**B Acetylcholine** A similar mechanism is apparently responsible for the arteriosclerotic changes found in the coronary vessels of animals treated with acetylcholine, as this substance produces a dilatation of the arterioles, a lowering of the blood pressure and, upon the administration of larger doses, a slowing of the heart action, causing thereby an impaired circulation and a vascular hypoxemia (Hall, Ettinger and Banting, Heinlein).

**C Nitrites** Recent experimental investigations on chronic nitrite poisoning of young rats, which were subjected for a period of 5 to 7 months to increasing amounts of erythrol tetranitrate, showed that an appreciable percentage of the animals thus treated developed at an extraordinarily early age extensive arteriosclerotic lesions in various organs (Hueper and Landsberg). These lesions consisted of medial degenerations of a hyalinizing, necrotizing and calcifying type, as well as intimal thickenings and perivascular fibrosis affecting the arteries of the brain, heart, lung, kidney and testes. It is noteworthy that similar vascular changes (coronary sclerosis, media degeneration

and intimal thickenings of myocardial arterioles, media degeneration and calcification of cerebral arteries accompanied sometimes by extensive perivascular fibrosis or accumulation of glia cells and brown pigment arteriolar sclerosis of the renal vessels etc) have been observed in chemical workers exposed to nitrites and showing during life the symptoms of chronic nitrite poisoning (excessively low blood pressure attacks of angina pectoris, bradycardia or tachycardia passive congestion of internal organs indigestion, diarrhea mental deterioration etc) Sudden death occurs often at a relatively early period of adult life with the symptoms of a coronary thrombosis or cerebral paresis (Meixner and Mayrhofer, Fischer, Lowy Laws, Ebright Robert Schulz, and others)

Commenting on the dynamics of the arterial pathology observed in experimental and occupational nitrite poisoning Hueper and Landsberg pointed out that nitrites cause by a relaxation of the walls of the peripheral arterioles with the resultant drop in blood pressure and the slowing of the blood flow a state of chronic passive congestion and stagnant hypoxemia Confirmatory evidence concerning the presence of a circulatory embarrassment was deduced from the fact that the rats subjected to chronic nitrite poisoning exhibited during the early part of the experiment a hemoglobinosis followed during the latter part by a persistent erythrocytosis of compensatory character, which was associated with a marked leucostatic leucocytosis in the peripheral vessels The conclusion drawn from this evidence was that an excessive dilatation of the vascular walls such as that resulting from a prolonged effect of nitrites causes a partial compression of the vasa vasorum and that the untoward effect produced by this condition upon the nutrition of the vascular wall especially its inner third is aggravated by an undue slowing of the blood flow and by a pathological lowering of the blood pressure This combination of factors impairing the oxygenation nutritive exchange and discharge of waste metabolites of the vascular tissues leads ultimately to the development of degenerative changes in the vascular walls, affecting particularly the arterial vessels of those organs (brain heart) most readily responding to the nitrites

It may be pointed out in support of this conception that chronic nitrite poisoning is characterized by the presence of degenerative and

fibrotic changes in the myocardium, such as those seen in connection with repeated administration of histamine and as the result of poisoning with hypertonic agents (adrenalin, parathyroid hormone, vitamin D, digitalis glycosides, etc.), indicating that a common fundamental causal mechanism is underlying the arteriosclerotic as well as the associated parenchymatous organic degenerative changes

D Carbon Monoxide Carbon monoxide is not known to be etiologically involved in the production of the ordinary type of arteriosclerosis. Brief mention, however, may be made of the degenerative and calcifying medial lesions and intimal proliferations found especially in the cerebral vessels as the result of accidental or experimental acute and, particularly, repeated carbon monoxide poisoning. The development of this condition is accompanied by a marked vasodilatation, a lowering of the blood pressure, an increased vascular permeability, and a hematogenic anoxemia due to the formation of carbon monoxide hemoglobin in addition to the stagnant anoxemia resulting from circulatory failure. The anatomical vascular effects associated with carbon monoxide poisoning and its resultant anoxic conditions are of significance in regard to the causal dynamics responsible for arteriosclerotic changes, as the vascular manifestations of carbon monoxide poisoning are very similar to those elicited by the administration of massive doses of vasculo-tonic agents, such as adrenalin, nitrites, histamine, etc., related to the genesis of arteriosclerosis

E Lowered Atmospheric Oxygen Experimental studies conducted by Buchner and Luft suggest that an excessive exposure to a reduced atmospheric pressure with the resulting hypoxemia may be the cause of arterial and myocardial degenerative lesions which are morphologically identical with those seen after the exposure to the previously mentioned anoxic agents. These authors found in rabbits and guinea pigs subjected to a lowered atmospheric pressure, corresponding to the conditions existing at about 8,000 meters altitude, myocardial degenerations and necroses and medial degenerations and necroses of the aorta in addition to degenerative changes in the brain. These observations are of particular importance from the standpoint of aviation medicine, especially as sudden deaths from coronary thrombosis in diseased coronary vessels have been observed in comparatively young pilots (White)



## COMMENT

The evidence presented supports the original thesis that the fundamental and general causal mechanism of degenerative arterial disease is an impaired nutrition and oxygenation of the vascular wall resulting in endothelial damage, increased intimal permeability, and the infiltration of plasma into the subintimal tissue followed by the proliferation of endothelial cells and the degeneration of the muscular and elastic elements of the media. If the plasma contains persistently or transiently pathologically large amounts of cholesterol or physicochemically related substances forming emulsions with the plasma there occurs a retention of this material in the proliferating endothelial cells with the ultimate formation of atheromas representing thus a special morphological variety of arteriosclerosis. The second morphological type of arteriosclerosis on the other hand is caused by highly excessive contraction or relaxation of the arterial wall through the action of hypertonic or hypotonic agents respectively giving rise to the development of primary medial necroses and calcifications. The secondary calcification of medial necroses is hastened and enhanced if the primary causal vasculotonic factor (parathyroid hormone vitamin D) produces at the same time a disturbance in the calcium metabolism or if a high blood calcium level is present normally as in herbivorous animals. Type and dose of the etiological agents thus influence to a certain extent the morphological type of the resulting arteriosclerotic lesion. It may be mentioned however that no fundamental distinction exists in the reactivity of elastic and muscular arteries as the direct lipid degeneration and hyalinization of the media of the muscular arteries and arterioles as well as the corresponding changes in polyvinyl alcohol atheromatosis are attributable to differences in the anatomical structure of these arteries from that of the large vessels. The morphological variations influence the penetrability of the lipoids or of the polyvinyl alcohol into the vascular wall. A sharp distinction between arteriosclerosis and arteriolosclerosis therefore cannot be made, especially as both types of vessels are often simultaneously involved. Whenever the arteriosclerotic process is found restricted to one kind of artery the type of the arteriosclerogenic agent its affinity for certain organic vessels and the intensity of its action or its dose combine in accounting for such a distribution.

The various etiological agents causing arteriosclerotic changes by interfering with the nutrition and oxygenation of the vascular walls may bring about this result by one of the following three effects

1 Chemically inert, film- and emulsion-forming agents (cholesterol, polyvinyl alcohol, methyl cellulose and, possibly, pathological, large molecular protein complexes) present in the plasma impair the gaseous and nutritive exchange in the interface of blood and vascular wall

2 Hypertonic agents cause not only an excessive densification of the vascular tissue with an exaggerated functional and metabolic stimulation of its component elements, but also a compression of the vasa vasorum resulting in an ischemic hypoxemia and aggravating the disturbances in the diffusibility of the vascular tissues to nutritive and waste metabolites

3 Hypotonic agents produce by an excessive dilatation of the vascular walls a compression of the collapsed vasa vasorum, a slowing of the blood flow and a lowering of the blood pressure, causing thereby a stagnant anoxemia in the vascular wall and an impaired gaseous exchange between the blood and the surrounding vascular tissues

The variations occurring in the regional distribution of degenerative arterial disease depend in part upon the nature of the etiological agent and the causal mechanism conditioned thereby. It is obvious that the physicochemical hematogenous disturbances are apt to produce more or less generalized atheromatous or arteriosclerotic lesions. However, clinical observations made in diabetics, as well as experimental findings, indicate that static conditions influence the frequency and severity of the resulting atheromatous responses. The relatively high incidence of such lesions in the arteries of the lower extremities in comparison to that of the upper extremities seems to bear out this statement (Lange, Joslin, Monckeberg, Morrison and Bogan). The more frequent and severe involvement by atheromatosis of the abdominal aorta in man, in contrast to the corresponding condition in the ascending part in animals points in the same direction. An exception seems to be presented by manual laborers such as street pavers, who show, according to Kulbs, a high incidence of arteriosclerosis of the arteries of the arms, suggesting that nutritive inadequacies of the vascular walls brought about by prolonged and excessive functional

strain entailed by an excessive demand for blood exert an arterio-sclerotic effect. A combination of mechanical frictional and hemogenic factors on the other hand, seems to be active in the production of the sclerosis of the pulmonary artery observed in connection with mitral lesions, patent foramen ovale, etc., resulting in an impaired pulmonary circulation. A similar circulatory effect produced by occupational activity accounts in glass blowers for the development of pulmonary sclerosis.

Causal agents operating through their influence upon the vascular tonus show often a regional, restricted type of response, unless they are active in highly excessive amounts or over very prolonged periods, as they display a limited affinity to certain organs or organ systems. Adrenalia as well as nitrates elicit most readily arteriosclerosis of the coronary, myocardial and cerebral vessels. Similar effects are produced in the coronary arteries by nicotine and in the cerebral and renal arteries by lead. Cobb and Blinn mentioned that clinical evidence indicates that people living under special emotional stress develop cerebral arteriosclerosis at an unusually early age. These selective cerebral actions of exogenous and endogenous arteriosclerotic agents are of significance as cerebral arteriosclerosis is in general of late occurrence.

The observations reported and conceptions advanced carry certain diagnostic therapeutic and preventive implications. It is obvious that a rational therapeutic management of arteriosclerotic individuals depends in part upon the determination of the etiological agent. This task is difficult in most instances because of the great complexity of our present day life. It may be more readily accomplished in cases of occupational arteriosclerosis such as is present in workers employed in the tobacco and chemical industries. The outstanding therapeutic procedure apparently capable of preventing the development or arresting the progress of arteriosclerosis or varying causation is represented by a maintenance of an adequate oxygen metabolism. Thyroid and iodine preparations have proved so far to be the most suitable agents for attaining this end particularly in cases in which an endogenous disturbance of the oxygen metabolism prevails. Experimental evidence indicates however that this therapy is ineffective in curing arteriosclerosis after the lesions have become established.

(Lundsgaard, Nielsen and Ørskov) It does not seem likely that a therapy which either counteracts more specifically the causal agent, or which eliminates it from further operation, can accomplish more. The relative importance of preventive measures in the control of arteriosclerosis is for these reasons becoming increasingly obvious.

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## STUDIES ON POLIOMYELITIS<sup>1</sup>

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The study of the epidemiology of human poliomyelitis has been handicapped by the lack of a suitable susceptible experimental animal. Until recently the only available animal was the rhesus monkey (1, 2), an animal which has very serious disadvantages. Firstly, it is expensive, thus limiting the amount of work possible. Secondly, it has by no means been established that the disease produced experimentally in this animal is the exact counterpart of the infection as observed in man. The chimpanzee (3) and the cynomolgus (4) monkeys, probably more satisfactory for experimental work, are still more expensive and not available in large numbers. The rhesus monkey, however, has proved to be invaluable in elucidating the etiology of human poliomyelitis. By its use it has been possible to show that the cause of poliomyelitis is a typical filterable virus with a marked affinity for the nervous tissues, particularly for the neurons of the anterior horns of the spinal cord. By means of ultrafiltration (5, 6) it has been shown that this virus is one of the smallest, sharing honors as the smallest known virus with that of foot and mouth disease. The diameter of the virus particle is in the neighborhood of 10 m $\mu$ . This fact excludes definitely from consideration in the etiology of the disease various micro-organisms such as streptococci (7) or other structures such as the globoid bodies (8), which have at one time or another been advanced as having etiological significance.

In the rhesus monkey the virus is strictly neurotropic. No evidence is available that it can infect and multiply in this animal in any tissue except that of nervous origin. This idea of strict neurotropism of

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the virus as shown in the rhesus monkey has colored the views of workers, particularly in the United States, as to the disease in man. Thus, it was generally assumed that in man, too, the only tissue susceptible to infection was nervous tissue, an hypothesis which required a great deal of ingenuity to substantiate. One of the striking features of poliomyelitis is that it is a disease chiefly of young children. This fact is emphasized by its common name, infantile paralysis. An explanation had, consequently, to be found for the relative resistance of the older age groups of the population. It was assumed that these had become immunized as a result of subclinical infection and, in keeping with the strict neurotropism of the virus in monkeys, that this infection was in the nervous system.

Evidence that the relative insusceptibility of older individuals was due to a previous immunizing infection was early forthcoming. Firstly, from the experimental side, it was shown that monkeys which survived an experimental infection developed antibodies which had the power of specifically neutralizing the virus of human poliomyelitis (9). Secondly, it was shown that in the serum of children convalescent from the disease similar neutralizing antibodies could be demonstrated (10). It was, consequently, reasonable to assume that the presence of such specific antibodies was due to a previous infection with the virus. Following this line of investigation, it was soon found that presumably normal individuals (11), that is, individuals who neither had suffered from an attack of poliomyelitis, nor, as far as could be determined, had had contact with a case of poliomyelitis, harbored these specific antibodies in their serum. The incidence of these antibodies was low in the younger age groups but reached close to 100 per cent in adults (12).

In attempting to solve the riddle of the epidemiology of the disease, two questions had to be answered: firstly, how does a child developing poliomyelitis contract the infection, and, secondly, how does the vast majority of the population become immunized. It was assumed that these two questions were simply two different ways of asking the same question: What is the portal of entry of the virus? A possible solution to this question was again furnished by experiments on rhesus monkeys, for it was shown early that an infection could be produced in this animal by the intranasal instillation of virus (13) and that virus



could be shown to be present in the nasopharynx of infected animals (14) The hypothesis was established that this was the portal of entry in man and as a corollary that the virus was spread from man to man by droplet infection In other words both entry and exit of the virus were through the upper respiratory tract As supporting evidence for this hypothesis it was shown that the virus of poliomyelitis could be demonstrated at times in the nasopharynx of patients suffering from the disease (15) A difficulty however was immediately apparent for epidemiological studies had shown that there was very little if any evidence of contact between cases Consequently, the source of infection other than that furnished by actual cases of the disease had to be found And in fact, it was shown with a great deal of difficulty that the virus of poliomyelitis could on occasion be isolated from the nasopharynx (16) or tonsils (17) of apparently normal individuals

Our interest in the study of the epidemiology of poliomyelitis dates from the discovery of a spontaneous disease in white mice closely simulating the cardinal features of human poliomyelitis (18)

Early in 1933 a mouse was found among our normal stock presenting a flaccid paralysis of the hind legs This animal was killed and portions of its brain and spinal cord were used for transmission purposes and for pathological study By intracerebral inoculation of other mice a similar condition was produced and the infection could be maintained indefinitely by serial passages in these animals Clinically the disease in mice is a replica of human poliomyelitis Following inoculation and an incubation varying in length depending upon the concentration and the strain of virus used the animals became paralyzed The paralysis was of the flaccid type thus indicating a lower motor neuron damage The degree of paralysis varied Sometimes only one limb was affected at other times the paralysis spread rapidly leading to the death of the animal In mice which lived the degree of paralysis became less individuals which were only slightly paralyzed apparently recovered completely On the other hand animals which were markedly paralyzed never recovered the full use of their limbs Marked deformities resulted with extreme emaciation of the permanently affected muscles Apart from the paralysis there were no other signs Only in the central nervous system could lesions

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of a more virulent strain. We were thus able to immunize mice successfully by inducing a clinically inapparent, as well as an apparent, infection of the central nervous system for we were able to show that mice inoculated intracerebrally with an almost avirulent strain nevertheless had an infection of the central nervous system. The proof of this was shown by isolating virus from the spinal cords of such animals as well as by pathological study.

Apart from the intracerebral method of immunizing animals we were able to demonstrate that mice which remained well following an intranasal instillation or an intraperitoneal inoculation of virus were rendered relatively insusceptible to a subsequent intracerebral inoculation. In neither instance was evidence obtained that the immunity produced was due to an infection of the central nervous system. The degree of this immunity depended on the size of the immunizing dose.

One of the most striking features of the experimental disease was the resistance developed with age by mice. Normal mice developed with age a relative resistance to an intracerebral inoculation or intranasal instillation. In attempting to assess the immunity produced by any experimental procedure the resistance developing with age had to be kept in mind. When two groups of normal mice of the same strain but differing in age were inoculated intracerebrally with a relatively avirulent virus the difference in the resulting morbidity and mortality was often striking. This resistance to experimental infection was developed rapidly in the younger age groups from birth up to 6 or 7 weeks of age but more slowly thereafter.

Before going on to a discussion of the natural disease let us summarize the findings of the experimental infection. From mice found spontaneously paralyzed a virus could be demonstrated which was transmissible in series by intracerebral inoculation to other mice. In all physical and chemical properties the virus resembled that of human poliomyelitis. Mice which had survived an infection of the central nervous system whether this was manifested by paralysis or not were rendered immune to a subsequent inoculation of the virus. By the intranasal or intraperitoneal inoculation of virus a relative immunity could be produced. Finally normal mice developed with age a relative resistance to the experimental disease.

Very little information is available as to incidence of the sponta-

be demonstrated. Histopathologically, the chief lesion was in the anterior horn cells of the spinal cord. There was an acute necrosis of the ganglion cells followed by neuronophagia. In the brain there were similar changes but to a much less marked extent. In both the brain and spinal cord perivascular infiltration was present. We were so impressed by the marked similarity, both clinically and pathologically, of this disease in mice and human poliomyelitis that we were tempted to name the newly discovered disease *mouse poliomyelitis*. To avoid a false impression that we had succeeded in transmitting the virus of human poliomyelitis to mice we named the disease *spontaneous encephalomyelitis of mice*.

Our early work was concerned chiefly with the properties of the virus and with the experimental disease. This work was rendered extremely difficult on account of the low pathogenicity of the strains of virus available at the time. Recently, however, we have isolated two strains of virus highly pathogenic and with these we have been able to work with greater assurance (19).

The properties of the virus of mouse encephalomyelitis so far determined are exactly like those of the virus of human poliomyelitis. Both are of the same size, both can be preserved in glycerin or at  $-76^{\circ}\text{C}$ , both retain their activity very poorly in the frozen and dried condition, both are resistant to the action of ether, both are inactivated readily by means of hydrogen peroxide, etc. I need not go into the complete list of similarities between these two agents. Suffice it to say that in their physical and chemical properties these two agents as far as can be determined, are identical.

In the experimental disease in mice certain fundamental properties of the virus were discovered. Apart from the intracerebral method of inoculation, mice could be infected by the intranasal as well as by the intraperitoneal, route. However the latter two methods of inoculation were successful only under certain conditions which depended upon the dose as well as virulence of the strain of virus used. Furthermore, certain immunological facts were determined. Thus mice which became paralyzed but lived were solidly immune to a subsequent intracerebral inoculation. Many mice inoculated intracerebrally with our less virulent strains although apparently remaining well, were rendered immune to a subsequent intracerebral inoculation.

large box. Breeding was allowed to go on so that we had a colony of mice of all ages. Into this colony mice found spontaneously paralyzed were placed at irregular intervals whenever such mice were discovered. This experiment was allowed to go on for several months, but we never observed a single case of the disease develop in our normal colony.

You will observe that up to this point the few facts which we had been able to establish concerning the epidemiology of the mouse disease were much like those known concerning human poliomyelitis. Both are diseases chiefly of young individuals in both there is an immunity developed with age and in both the active case does not seem to act as a focus in the spread of the disease.

Our study had reached this point when an observation made by Dr P. K. Olitsky (20) furnished us with a lead on which we have done a great deal of work. He found that in the intestinal contents of apparently normal mice an agent could be recovered which in all respects resembled the virus of encephalomyelitis of mice. Clinically and pathologically the two viruses were identical. By cross immunity tests he was able to show that there was reciprocal immunity. This discovery seemed to offer the means of working out a rational epidemiology of the disease and we immediately undertook to determine the incidence, duration and site of this intestinal infection. We were soon able to show that all of our stocks of mice were infected (21). This was done by inoculating mice intracerebrally with filtrates made from feces collected in the boxes containing our normal mice. In each instance several of the inoculated mice after an incubation period of from 12 to 29 days became paralyzed. From such affected animals the infection could be maintained by serial mouse brain-to-brain passage. In order to obtain a rough idea of the actual incidence and duration of the infection individual mice were placed in clear jars and fed on sterile food and water. At the bottom of each jar was a wire stage on which the mouse rested. In this manner contamination of the mouse's food by its own dejecta was reduced to a minimum. Jars and wire stages were changed daily. Fecal specimens could be collected from each mouse whenever desired and tested for the presence of virus. Fifteen mice, all approximately 6 weeks of age, picked at random from our normal stock animals and apparently in perfect

neous disease in mice Since the original discovery of the virus we have seen spontaneous cases in stock mice every year The incidence of spontaneously paralyzed mice is extremely low Although in our laboratory we use many thousands of mice annually, the number observed every year is only about four or five So seldom are spontaneously affected animals seen that at one time we thought the disease was purely accidental No evidence of any seasonal incidence is available All spontaneous cases observed have been in young animals approximately 3 to 7 weeks of age This statement is based on the fact that all paralysis so far found has occurred in mice shortly after they have been delivered to us from the dealers, who supply us regularly with mice from 3 to 6 weeks of age At times mice under experimentation with other viruses have developed a spontaneous infection of the central nervous system with this virus, and this has occurred only in young animals On different occasions we have kept several thousands of normal mice under observation for various periods of time and have never observed a single case of spontaneous paralysis in an old mouse Recently we have kept 1500 normal mice under observation for 6 months At the beginning of the experiment the mice were all approximately 6 weeks of age During the 1st week of observation a single case of paralysis occurred and none thereafter I shall have occasion later to refer to this experiment

In our early attempts to elucidate the epidemiology of this disease we undertook various types of contact experiments Groups of normal mice were placed in contact with others artificially infected by either intranasal or intracerebral inoculation of virus In no instance did a normal contact mouse develop the disease of the central nervous system Furthermore, the contact mice when tested at the conclusion of the experiment were no more resistant to an intracerebral inoculation of virus than the control mice The controls were of the same strain and age, had been kept under the same environment, and differed only in that they were not exposed to infected mice From these experiments it was obvious that mice with an experimental infection of the central nervous system did not serve as foci of infection It was thought, however, that the conditions of the experiments were in certain ways highly artificial Consequently, in order to simulate more natural conditions, a group of mice of both sexes was kept in a

stomach, small intestine, cecum, large intestine, kidney, spleen, liver, heart, and lungs. The only organ in which virus was shown to be present was the small intestine. No evidence was obtained of any virus in the head, thus ruling out as the source of virus in the intestine such organs as the salivary glands, mucosa of mouth, and pharynx.

We have performed several experiments along similar lines, each time hoping to add a little to our knowledge of the distribution of the virus in normal animals. Apart from the small intestine, the only organ where the virus can be demonstrated with any degree of regularity is the mesenteric lymph node (22). In nine out of twenty-four mice these glands have been positive. Efforts at determining the site of virus multiplication in the intestines have not given clear-cut results. As a rule, the contents of the small intestine seem to contain more virus than the washed intestinal walls. The possibility, however improbable, that the source of virus shown to be present in the small intestine originated in some manner in the intestinal contents had to be entertained. Although this possibility has not been excluded, the evidence to date points to the intestinal mucosa as the site of virus regeneration. In experiments designed to determine in what portion of the intestinal wall the maximum concentration of virus occurred, attempts were made to test various anatomical structures separately. Thus the mucosae were separated by scraping, then the lymph follicles were dissected out. The three portions thus obtained, the mucosa, lymph follicles, and what was left after the removal of the first two, were tested separately for virus content. The greatest amount of virus was found in the mucosa. Small amounts of virus were found in the rest of the intestinal wall, which might have been due to incomplete removal of the mucosa. Virus was frequently found in the lymph follicles, some or all of which might have been due to contamination from the mucosa during the process of dissecting out. However, on one occasion the intestinal lymph follicles were the only sites in the body where virus was found. It was also shown that more virus was present in the upper portion of the small intestine than in the lower. The contents of the large intestine, as was to be expected, contained virus. However, no evidence was found that the walls of this organ contained any virus.

Summarizing our findings of the distribution of virus of mouse

health were placed in isolation jars. Virus was found to be excreted in the feces of ten of these animals. To determine the duration of this infection, feces were collected at intervals and tested for the presence of virus. The longest time after isolation that virus was recovered was 53 days. This experiment, small as it was, showed that approximately two-thirds of normal mice 6 weeks of age picked at random were excreting virus in their feces for a considerable period of time. The next step was to determine the source of this virus.

In our first experiment three normal mice 6 weeks of age were killed, and the various organs were pooled and tested for the presence of virus. Brains, spinal cord, liver, lungs, and spleen were entirely free from virus. In the gastro-intestinal tract, however, virus was definitely shown to be present in all four portions tested, the stomach, small intestine, cecum, and large intestine. The conclusion seemed warranted that in this experiment the virus was shown to be present throughout the gastro-intestinal tract. However, as these mice had not been kept in isolation and fed on sterile food, it seemed possible that some or all of the virus shown to be present might have been due to the mouse having ingested contaminated food.

Consequently, in the next experiment we chose a mouse which we had kept in isolation and fed on sterile food and water for 21 days. The infectivity of stomach, small and large intestines was tested. The results of this experiment confirmed the first one. Virus was shown to be present in all portions of the gastro-intestinal tract tested. This experiment thus gave conclusive evidence that the virus must have been derived from the animal and not some outside source. No conclusion, however, could be drawn as to the source of the virus within the animal. Any virus in the gastro-intestinal tract might quite reasonably have come from some focus above the stomach such as the nasal mucosa or salivary glands. Consequently, in the next experiment we tested this point. A mouse kept in isolation and known to be excreting virus was killed. Following removal of the brain the head was severed from the body. The head, containing all the salivary glands, etc., but not the skin, was ground thoroughly in a mortar, and the suspension after centrifugation was filtered. The filtrate was used to inoculate twenty-five mice intracerebrally. In addition to that of the head, the infectivity of the following organs was tested: brain,



intestinal infection we kept under observation a colony of 1500 mice. These were placed in cages of 75 each. One mouse in fifteen was marked and used for the collection of fecal specimens throughout the experiment. All mice were 6 weeks old at the beginning of the experiment and were so-called Swiss mice. Fecal specimens were obtained from the marked mice when they were 6 weeks old, that is, at the beginning of the experiment, and again when the mice were  $2\frac{1}{2}$ ,  $4\frac{1}{2}$  and  $7\frac{1}{2}$  months old. To collect the fecal specimens the routine was adopted of keeping the mice in individual jars with wire stages for 2 days. During this time they were fed on autoclaved food and boiled water. At the end of this period each mouse was transferred to a new clean jar, again containing a wire platform, and the feces were collected. The mouse was then returned to the colony. In this way we hoped to exclude the possibility that any virus present in the feces could have been due to the eating of contaminated food immediately before the fecal collection. Each fecal specimen was tested for the presence of virus by the intracerebral inoculation of a group of twelve mice with a centrifuged suspension of the feces. Of the 100 marked mice selected for this study, 69 were alive at the end of the experiment. In the feces of all but two virus was demonstrated at one time or another.

The exact analysis of our results is difficult since on several occasions a mouse proved infective on nonconsecutive tests. This might be explained by assuming that these mice may have lost their infection and then later became reinfectd. Although this possibility cannot be excluded, we feel that such results can be more reasonably explained by the inadequacy of our technique for the demonstration of virus in feces. Particularly towards the end of the experiment the concentration of virus in infected feces was so low that on an average only two out of twelve mice inoculated became paralyzed. Consequently our figures for the number of mice excreting virus in their feces are, in all probability, too low and the mice in which fecal examination proved positive on nonconsecutive runs represent, in all likelihood, a continuous infection.

Of the 69 mice which lived throughout and on which we had four fecal examinations, 45 (65 per cent) were shown to be infected on the first examination. One month later, on the second test, an additional

encephalomyelitis in normal mice at approximately 6 weeks of age, we can say that the infection is probably one of the mucosa of the small intestine. From here there is a tendency for the virus to invade the body by the lymphatic vessels, by which it is transported to the mesenteric lymph nodes. This latter finding affords clear evidence that, at least during one stage of the infection, the virus is able to invade the animal organism and thus presumably acts as an antigen for the production of antibodies. I shall return to this subject later.

The distribution of virus in mice found spontaneously paralyzed was determined on five occasions. Virus was found only in the central nervous system and intestinal tract. The amounts in the intestinal tract were, on the whole, small and no more than in infected non-paralyzed mice. In two instances no virus could be demonstrated in the intestinal wall, while small amounts were, nevertheless, found in the intestinal contents. On account of the extreme rarity of spontaneous paralysis in mice, our observations on the distribution of virus in such animals are limited. However, as far as our studies go, it would seem that the distribution is the same as in normal animals except that the central nervous system is infected in addition. In the study of these mice found spontaneously paralyzed we found no evidence of how the virus reached the central nervous system. No virus could be demonstrated in the nasal mucosa on the two occasions when this was tested. The characteristics of the virus strains isolated from the gut of normal animals are, as far as can be determined, the same as those of the strains derived from the central nervous system of mice found spontaneously paralyzed. It would seem, therefore, that the infection of the central nervous system is not due to an unusually virulent strain of virus. Involvement of the central nervous system is apparently an accident occurring early in the infection of the small intestine.

We come now to a more detailed consideration of the incidence and duration of the intestinal infection. Oltzky had shown that fetal mice and newborn mice are not infected (23). Suckling mice were likewise found to be free from virus. At 20 days of age the demonstration of virus was irregular. In all tests on mice 1 to 2 months of age the agent could be demonstrated.

In our experiment to determine the incidence and duration of the

through the placenta to the embryo. Young mice are consequently born with a passive immunity. This passive immunity wears off during the suckling period and is followed by an active immunity as a result of the intestinal infection acquired shortly after weaning.

These in the main, are our findings to date. Several important points have still to be determined. We assume that infection is acquired by mouth. This has not been proved definitely but seems to us a reasonable assumption. Likewise we do not know why with the infection being so universal only a very small minority of mice develop an infection of the central nervous system. Nor do we know by what route the virus invades the central nervous system from the intestine. There are several possibilities. The first way is via the lymphatic pathways to the mesenteric lymph nodes then to the blood and finally to the central nervous system. This does not appear likely. The second and to us more probable way is via nervous pathways to the central nervous system.

In brief it seems that in a colony of white mice the infection with the virus of mouse encephalomyelitis is very widespread. Few, if any mice escape. As far as can be determined mice do not suffer any harm from the intestinal infection. The duration of the intensity of the infection seems to be determined by the genetic make-up of the mice. The albino mouse cannot be considered as a true representative of the wild house mouse from which it is derived. It is probable that the continued inbreeding of the albino mouse has produced an individual which genetically differs in many respects from the wild stock. That this is so is shown by the fact that the silent intestinal infection with the virus of mouse encephalomyelitis is rare in the wild mouse. We have examined numerous wild mice for the presence of this virus without success. However, Dr. Olitsky has recently been able to isolate a strain of the virus from the intestines of wild mice caught in the Rockefeller Institute.

We have been so impressed with the close similarity between our mouse disease and human poliomyelitis that we have spent considerable time and effort to determine whether there was any immunological relation between the two viruses. When we first discovered our virus the only animal at the time known to be susceptible to the virus of human poliomyelitis was the monkey. We have at one time

16 (23 per cent) were found infected. At the time of the second test the mice were  $2\frac{1}{2}$  months old, and a total of 61 of the 69 mice (88 per cent) was shown to be infected. Four mice were shown to be infected for the first time on the third test, at an age of  $4\frac{1}{2}$  months, and two mice only on the final test at  $7\frac{1}{2}$  months. In two mice virus was never demonstrated.

Since it is known that mice at the time of weaning, at 2 weeks of age, are free from virus, the maximum infection rate occurs in the month immediately following weaning. The highest incidence in our experience is at the age of 6 weeks when 65 per cent were excreting virus in their feces. From this point the incidence falls very gradually until at the age of  $7\frac{1}{2}$  months the incidence is 54 per cent. You will see that in our colony of mice the incidence of individuals excreting virus during an observation period of 6 months is never less than 50 per cent. Under these circumstances it is indeed a remarkable fact that cases of involvement of the central nervous system are so infrequent. In our experiment in which we observed a colony of 1500 mice for 6 months, only one mouse showed signs of involvement of the central nervous system. This occurred at the beginning of the experiment when the mice were only 6 weeks of age.

With the infection so universal, it seemed of interest to determine whether normal mice develop with age specific antibodies. We were immediately confronted with a difficulty, for in order to determine whether or not a given mouse serum contained specific neutralizing antibodies, we had to inoculate mixtures of serum and virus into mice, all of which were probably already infected. To overcome this difficulty, we used mice 3 weeks of age, an age when the incidence of intestinal infection was still low. In this manner we obtained evidence that in the serum of mice before weaning there were demonstrable antibodies. With the exception of the serum from mice 3 weeks of age, all the older age groups showed specific antibodies. The interpretation we placed on these findings is briefly as follows. Since nearly all adult mice have been shown to have an intestinal infection and since we have shown that the virus can invade the animal organisms, it is reasonable to assume that as a result specific antibodies are produced. Now the mouse belongs to the group of animals, which also contains man and monkeys, in which antibodies pass from the mother

than 80 serial passages. At intervals this mouse passage virus was tested for its pathogenicity for cotton rats and rhesus monkeys. The original virus was highly pathogenic for both species in intracerebral inoculation. It was noted that the virus propagated in mouse brains rapidly lost its pathogenicity for the monkey. Virus from the first and third mouse brain passages produced paralysis in all of four monkeys. Only one out of two monkeys inoculated with the fifth, eighteenth, and twenty-first passages developed poliomyelitis. None of eight monkeys inoculated intracerebrally with material from the fifty-first to the fifty-fourth mouse brain passages developed any signs of poliomyelitis. Prolonged passage of the Lansing strain of poliomyelitis had consequently completely attenuated the virus for the rhesus monkey. A similar attenuation was noted in the pathogenicity of this virus for cotton rats. All of twenty cotton rats inoculated with material from the first to the twenty-first serial brain passages died. Only nine of twenty-one cotton rats inoculated with the fifty-first to the fifty-fourth passages died, whereas, only one of thirty cotton rats inoculated with the seventy-first mouse brain passage showed any signs of infection. Prolonged passage in mice of the Lansing strain produced a strain of virus which was pathogenic for mice, only slightly pathogenic for cotton rats, and nonpathogenic for monkeys. In all these respects this attenuated human poliomyelitis virus now resembled a strain of mouse encephalomyelitis (25).

Following the announcement by Armstrong of the susceptibility of the cotton rat to the Lansing strain of human poliomyelitis, we immediately tested the susceptibility of this animal to several of our strains of mouse encephalomyelitis. We found that our more virulent strains were moderately pathogenic, producing a disease at times indistinguishable from that produced by the Lansing strain. This infection could be maintained in series in cotton rats by brain-to-brain passage. A considerable number of cotton rats which survived the intracerebral inoculation of the virus of mouse encephalomyelitis proved to be resistant to a subsequent inoculation of the Lansing strain of human poliomyelitis. In a similar manner we were able to show that mice which had become paralyzed but lived following an infection from the virus of mouse encephalomyelitis were made relatively resistant to the Lansing strain. We do not believe that this cross im-

or another inoculated many rhesus monkeys with various strains of the virus of mouse encephalomyelitis. They neither showed any susceptibility to the mouse virus nor did they develop any immunity to a subsequent inoculation of human poliomyelitis.

Recently Armstrong (24) succeeded in obtaining a strain of human poliomyelitis which is pathogenic not only for monkeys but also for cotton rats and mice. Dr. Armstrong kindly sent us the Lansing strain of poliomyelitis, and we were able to confirm this worker's findings. The material received by us, the thirty-fourth serial passage of this strain in cotton rats, was pathogenic for monkeys as well as mice. In monkeys the clinical picture was consistent with that produced by other strains of human poliomyelitis. Monkeys which became paralyzed with the Lansing strain of virus were resistant to a subsequent inoculation of a known human strain of poliomyelitis. Furthermore, the Lansing virus was neutralized both in mice and in monkeys by poliomyelitis immune sera. The converse was also true, namely, the serum from a monkey convalescent from an infection with the Lansing strain had the power of neutralizing another strain of human poliomyelitis virus (25). These are the methods available for identifying a strain of virus as that of human poliomyelitis. Since the Lansing strain fulfills these requirements, we must conclude that this strain is either one of human poliomyelitis or at least very closely allied to it.

Individual mice infected with the Lansing strain are clinically almost indistinguishable from mice infected with the virus of mouse encephalomyelitis. However, the course of the disease in the two is entirely different. The mouse virus is distinguished by a remarkably uniform course of infection. So uniform is the incubation period for a given strain that this has been utilized as a measure of the concentration of the virus in a given preparation (26). This does not hold true for the Lansing strain. However, in spite of this irregular action of the virus in mice, these animals have proved invaluable in performing neutralization tests (27).

Since the beginning of our work with the Lansing strain we have undertaken a rapid serial passage of this virus in mice. As soon as a mouse was noted to be paralytic, usually in the 2nd or 3rd day after inoculation, its cord was removed and used to inoculate the next group of mice in the series. To date we have carried the virus through more

central nervous system has no advantage. This must be looked upon as an abnormal habitat and purely accidental in nature.

We were motivated in spending a great deal of time in attempting to elucidate the epidemiology of the spontaneous encephalomyelitis of mice chiefly because we were able to use as experimental animals the normal hosts of the virus. It was unfortunate that many ideas about the epidemiology of human poliomyelitis were formed from observations on an abnormal host, the monkey. The tendency recently for the students of the human disease has, I am glad to say, returned to the study of the disease in man, and the recent very important findings are beginning to fit into a general plan which appears to be much like that which we have been able to establish for the disease in mice.

Let us enumerate briefly what one should expect if the epidemiology of human poliomyelitis follows the basic pattern of the mouse disease. Firstly, one would expect that for every clinical case there should be many individuals who never show any signs but, nevertheless, become immunized. Secondly, the occurrence of the disease should follow more the pattern of those diseases such as typhoid or dysentery which are acquired through the gastro-intestinal tract and not that of diseases transmitted by droplet infection. Thirdly, the distribution of the virus in man dying of the disease should be essentially that which we have described for the mouse, and, finally, one ought to be able to demonstrate the presence of virus in the stools of perfectly normal individuals.

Now all recent findings tend to substantiate this hypothesis. It has been known for a long time that poliomyelitis is a disease of childhood and that adults are resistant. Furthermore, specific antibodies can be shown to be present in the blood of normal individuals who have never had poliomyelitis. The exact incidence of these antibodies in the different age groups is unknown. An inexpensive experimental animal susceptible to the virus of human poliomyelitis only recently became available when Armstrong discovered that mice are susceptible to the Lansing strain of poliomyelitis. By means of a neutralization test similar to the one used by Armstrong, we have recently reinvestigated this subject. Our tests have served to confirm previous findings. Thus, in a series of tests done with the sera of infants we could show that all children in the first few months of life born of mothers with

munity is specific for the reason that, in mice at least, the resistance developed seems to depend on the actual presence of paralysis. Mice which were immunized against the virus of mouse encephalomyelitis by the intraperitoneal injection, although rendered immune to the homologous virus, were not appreciably more resistant to the Lansing strain than normal mice. Furthermore, we have never been able to show any serological relation between the two. The serum from a monkey or cotton rat immune to the Lansing strain of poliomyelitis has no neutralizing action on the virus of mouse encephalomyelitis and, conversely, mouse sera containing antibodies for the mouse virus have no action on the Lansing strain of poliomyelitis (25).

Let us summarize our knowledge of the pathogenicity of these various poliomyelitis-like viruses. Firstly, the great majority of strains of viruses isolated from man are pathogenic for monkeys, but not for cotton rats or mice. Only one strain, the Lansing strain, of human poliomyelitis has been definitely shown to be pathogenic for all three species of animals, namely, monkeys, cotton rats, and mice. This latter strain by serial passages in mice has been modified so that it is pathogenic for mice but only slightly, if at all, for cotton rats and monkeys. This strain is still immunologically human poliomyelitis. And finally, we have the strains of viruses isolated from normal mice pathogenic for these animals, only slightly for cotton rats, but not at all for monkeys. What is the significance of these findings? With our present lack of knowledge it is impossible to say. However, to hazard a guess, it is possible that there is a whole group of viruses which are able to produce a poliomyelitic type of disease in various species of animals. At present we know of only two, human poliomyelitis and mouse encephalomyelitis. The Lansing strain might be considered as bridging the gap between the two. We may be dealing with a group of viruses like the pox group, which all bear some resemblance to each other, and at times even show some immunological relation as exemplified by the fact that cowpox will effectively immunize against smallpox.

Human poliomyelitis presumably has in common with mouse encephalomyelitis the characteristic of being almost a perfect parasite, that is in the vast majority of infections the host is not harmed in any way. From the point of view of the virus, the invasion of the



It is almost axiomatic that in virus diseases the presence of specific antibodies is proof of a previous infection with that virus (33). We are confronted therefore with the unsolved mystery of the site of this infection. How prevalent this must be is emphasized by the fact that these antibodies have been shown to be present in the blood of the great majority of adults in all parts of the world. Evidence that the site of infection in man is in all probability in some part of the alimentary tract has been accumulating during recent years (34). Thus the virus has been isolated from the stools of individuals apparently in perfect health who had been in 'contact' with cases of poliomyelitis (35). Also virus was demonstrated in the stool of a girl 123 days after she had an abortive attack of the disease (36). In patients with poliomyelitis (37) numerous observations are available that it is relatively easy to isolate the virus from the stools. Coupled with this is the finding that poliomyelitis has been demonstrated in sewage (38).

In studies on the distribution of the virus of poliomyelitis in fatal human infections the noteworthy findings to date are the presence of virus in some part of the alimentary tract, in the mesenteric lymph nodes (39) and in certain portions of the central nervous system. Of equal significance is the absence of virus in the nasal mucosa and olfactory bulbs (40). Pathological study of the olfactory bulbs in fatal cases of poliomyelitis has not revealed any changes (40). Good evidence that this is not the portal of entry of the virus. I could enumerate more evidence in support of the theory I have outlined, evidence obtained from human cases of poliomyelitis, from epidemiological studies and from observations in experimental animals (41) but I think I have presented enough observations to show that my hypothesis is a reasonable one.

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neutralizing antibodies in their blood likewise show these antibodies (25) In the blood of children from 6 months to 1 year these neutralizing antibodies are, as a rule, not present The presence of antibodies in the very young children must be considered as due to passive immunity from the mothers This passes off with time so that children older than 6 months do not, as a rule, show these antibodies, but at about 1 year of age antibodies again appear and the incidence increases with age

Although these observations only confirm previous findings (28), I am emphasizing this aspect of our subject for the reason that there has been a tendency to minimize the significance of neutralizing antibodies in the blood of normal individuals This is due chiefly to two reasons Firstly, it was shown experimentally that monkeys, although having antibodies in their blood, are not always immune to an intranasal or intracerebral inoculation of virus (29), and, secondly, because it has been found that in some children with a manifest infection of the central nervous system antibodies could, nevertheless, be demonstrated in the blood (30) From these two observations it was concluded that neutralizing antibodies do not prevent an infection

Now it seems to me that neither of these observations presents any valid criticism of the hypothesis that the presence of antibodies does not play an important rôle in the defense mechanism The experiments in monkeys are highly artificial in character Neither *intracerebral* nor *intranasal* inoculation of virus represents the *normal* portal of entry of the virus The finding of antibodies in the blood of some children with poliomyelitis is in fact, what one would expect if the infection were only secondarily one of the nervous tissue Thus, it is a well established fact that in infections with so-called neurotropic viruses, which invade the nervous system only after a systemic infection, antibodies are often present in the blood at the time of nervous system involvement (31) What seems to be important here is the titer of antibodies present in those children developing poliomyelitis It may be that we have a set of circumstances here such as has been demonstrated for influenza A in which the titer of the antibodies is the significant feature (32) It seems to me the most reasonable interpretation of the presence of antibodies is that this is due to an infection with the virus of poliomyelitis and that they furnish an index of immunity

## INFECTIOUS POLYNEURITIS

### INFECTIOUS NEURONITIS, ACUTE POLYNEURITIS WITH FACIAL DIPLEGIA, GUILLAIN-BARRÉ SYNDROME, LANDRY'S PARALYSIS, ETC.<sup>1</sup>

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"Infectious polyneuritis" is a disease entity which is not well known although its occurrence is not uncommon. There are several reasons why physicians are unfamiliar with the condition—the chief being the sterility of all investigation aimed at its etiological elucidation. Other factors are the collapse of an eponym (Landry's Ascending Paralysis<sup>2</sup>), the multiplicity of synonyms by which this type of neuritis is known, and the variance in the pathology of the disease from case to case as it has been described in the literature.

Synonyms in medicine seem to appear in inverse proportion to the information at hand on a given subject. Neurological terminology abounds with them to the despair of the student. A few of the synonyms for "infectious polyneuritis" are listed in a footnote so that there will be no question about the condition with which this article is concerned.

This presentation will deal with a description of the clinical features of the disease and a rather comprehensive study of the pathology of three cases. It will be demonstrated that significant changes may be found in the peripheral and central nervous systems, contrary to the

<sup>1</sup> Work aided by a grant from the Rockefeller Foundation.

<sup>2</sup> Brown (1938) analyzed Landry's original case and came to the conclusion that the etiological factor was a nutritional deficiency. The neuritis was precipitated by dietary insufficiency bordering on starvation in an individual with a severe infection. Brown pointed out that Landry's case evidently was nothing other than beriberi polyneuritis.

<sup>3</sup> Acute febrile polyneuritis, acute infective polyneuritis, infective neuronitis, polyneuritis, motoneuronitis, acute polyneuritis with facial diplegia, acute ascending paralysis, Landry's ascending paralysis, Guillain-Barré syndrome.

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## INFECTIOUS POLYNEURITIS

### INFECTIOUS NEURONITIS ACUTE POLYNEURITIS WITH FACIAL DIPLEGIA, GUILLAIN-BARRÉ SYNDROME, LANDRY'S PARALYSIS, ETC <sup>1</sup>

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"Infectious polyneuritis" is a disease entity which is not well known, although its occurrence is not uncommon. There are several reasons why physicians are unfamiliar with the condition: the chief being the sterility of all investigation aimed at its etiological elucidation. Other factors are the collapse of an eponym (Landry's Ascending Paralysis<sup>2</sup>), the multiplicity of synonyms by which this type of neuritis is known, and the variance in the pathology of the disease from case to case, as it has been described in the literature.

Synonyms in medicine seem to appear in inverse proportion to the information at hand on a given subject. Neurological terminology abounds with them to the despair of the student. A few of the synonyms for "infectious polyneuritis" <sup>3</sup> are listed in a footnote so that there will be no question about the condition with which this article is concerned.

This presentation will deal with a description of the clinical features of the disease and a rather comprehensive study of the pathology of three cases. It will be demonstrated that significant changes may be found in the peripheral and central nervous systems, contrary to the

<sup>1</sup> Work aided by a grant from the Rockefeller Foundation.

<sup>2</sup> Brown (1938) analyzed Landry's original case and came to the conclusion that the etiological factor was a nutritional deficiency. The neuritis was precipitated by dietary insufficiency bordering on starvation in an individual with a severe infection. Brown pointed out that Landry's case evidently was nothing other than beriberi polyneuritis.

<sup>3</sup> Acute febrile polyneuritis, acute infective polyneuritis, infective neuronitis, polyneuritis, motoneuronitis, acute polyneuritis with facial diplegia, acute ascending paralysis, Landry's ascending paralysis, Guillain-Barré syndrome.

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26	8	MA	None appar- ent	Numbness and parae- sthesia	Yes	Arms 0 Legs 0	Pain, tenderness, in- paired vibration and position	1 under jaw	DI plegia	Par- thl	Normal	No	No	215	2 L	110	No effect	Well
5	9	AB	Frequent colds	Sudden weakness	Yes	Arms 0 Legs 0	?	No	No	No	No	No	No	150	2 I	101	Not given	Well
7	10	SD	Meningeal 21/57	Pain 6/1/57	No	Arms -1 Legs 0	Tenderness, pain and hyperesthesia	Illat hypal- gesia, motor weakness	DI plegia	Com- plete	Normal	Yes	Yes	"In- creased"	2 L	113	Not given	Well
21	11	NI	Auto accel- erant 9/1/57	Weakness 10/1/57	No	Arms 0 Legs 0	Tenderness, pain, numbness, in- paired touch and vibration	Illat motor weakness	Left	No	No	No	No	100	1 I	100	Relief of pain	Weakness present 3 years
62	12	CS	Cold myalgia 10/ 15/55	Numbness, paraesthesiae 11/12/55	No	Arms -0 Legs -0	Tenderness, pain, numbness, in- paired vibration	No	?	No	No	No	No	"Normal"	15 I, 19 I	Not done (Family 2 I)	Not given	Well
1	13	LI	Variella 12/ 6/59	Pain and weakness 12/21/59	Yes	Arms 0 except ra- dial 0 Legs 0	Pain	No	DI plegia	Com- plete	Na	No	No	115	2 I	112	Relief of pain	Well
18	14	JH	None appar- ent	Pain and weakness	Yes	Hypers- thesia in involuntarily involuntarily at one time or another	Pain, tenderness, paraesthesiae, All sensory modalities involved at one time or another	Illat motor hypalgnesia Pain	DI plegia	Par- thl	Normal	No	Yes	115 180	0	32 70	Not given Vitamin 1	Well
65	15	LS	"Parque- nia" fever Pain, June, 1910	Weakness, left, 1910 Pain, June, 1910	Yes	Arms 0 Legs 0	Pain, tenderness loss of pain, touch, vibration, position	No	Left	Na	No	No	No	150	26 I	115	Slight relief of pain Given vit- amin 1	Unimpaired to date
22	16	W	Variella 6/ 15/50	Pain and weakness 7/ 5/50	Yes	Arms 0 Legs 0	Pain, numbness, tenderness, loss of touch, pain, vibra- tion and position	Illat motor hypalgnesia right face Absent cor- neal reflexes	DI plegia	Par- thl	Normal	Yes	Yes	210	5 L	102 112	Relief of pain Given Vitamin 1,	Well

Note: All patients showed a progressive proximal thoracic quadriplegia

TABLE 1

Data on sixteen patients with "infectious polyneuritis," all of whom had progressive, proximal, flaccid quadriplegia

Twelve of these patients had throat cultures and in only two were Klebs-Löffler bacilli found. These organisms were proven to be avirulent

Data on sixteen patients and in only two were Klebs-Löffler bacilli found																			
Twelve of these patients had throat cultures and																			
Case	Age	Color and sex	Recent illness	Initial nervous symptoms	Headache	Tendon reflexes	Sensory signs and symptoms	CRANIAL NERVE INVOLVEMENT							CEREBROSPINAL FLUID			EFFECT OF THIAMIN	RESULT
								Fifth nerve	Facial palsy	Palatal paralysis	Voice disturbance	Respiratory difficulty	Dysphagia	Initial pressure	Cells per mm <sup>3</sup>	Total protein, mg per cent			
1 JS	10	W M	Cold and "rheumatism" 2/1/10	Pain in back and legs 2/13/10	Yes	Arms—0 Legs—0	Pain and tenderness Sensory exam not done	Bilat motor weakness	Di plegia	Partial	Hoarse, nasal	Yes	Yes	170	3 L	125	Relief of pain	Died 2/21/10	
2 AM	16	W I	Cold and myalgia 2/15/10	Numbness in legs 3/7/10	Yes	Arms—0 Legs—0	Pain, tenderness, paresthesia in paired touch, vibration and position	Tenderness of jaws Bilat motor weakness	Di plegia	Complete	Hoarse, nasal	Yes	Yes	150	0	80	Not given	Died 3/11/10	
3 GI	36	W M	Cold 2/11/39	Pain in calves 2/26/39	No	Arms—0 Legs—0	Pain, numbness and tenderness in paired vibration	Hypalgnesia, left Bilat motor weakness	Di plegia	?	Nasal	Yes	Yes	190 250	0 1 L	130 75	Given temporarily	Died 3/11/39	
4 AM	25	W M	Cold	Pain and tingling	No	Arms—0 Legs—0	Pain, tenderness, paresthesia in paired touch, vibration and position	?	Di plegia	Complete	Nasal	Yes	No	"Normal"	0	100 200	Not given	Well	
5 IN	4	W M	Cold and myalgia 2/20/39	Paresthesiae 3/1/39	Yes	Arms—0 Legs—0	Pain, numbness, tenderness, and paresthesia in paired touch, vibration and touch	Sore jaws	?	No	No	No	No	160	0	110	Relief of pain	Well 4/1/39	
6 JG	6	W M	None apparent	Pain and stumbling	Yes	Arms—0 except biceps—0 Legs—0	Pain and tenderness in paired touch, and pain	No	Di plegia	No	Nasal	No	No	220	0	100	No effect	Well	
7 IW	32	W M	None apparent	Pain in calves	No	Normal	Pain and tenderness	No	I left	No	No	No	No	"Normal"	0	180	Not given	Well	



focusing attention on the possibility of the involvement of the seventh nerve in this disease. Guillain, Barré and Strohl (1916) were the first to note the high protein and low cellular content of the cerebrospinal fluid ("albumino-cytologic dissociation") in this disease. They also stated that the prognosis of the disease was favorable. In fact, Guillain (1936) separated his cases from those having a fatal result preferring to believe that they were afflicted with a distinct morbid process. Since 1916 the syndrome has been known in France under the modest and comparatively innocuous term of the "Guillain-Barré Syndrome." Under the heading of "acute febrile polyneuritis," Gordon Holmes (1917) discussed the clinical course of twelve patients and presented a pathological study in two of them. A most comprehensive and illuminating work on the subject is the monograph by Bradford Bashford and Wilson (1918). Bradford clearly described the clinical phenomena in thirty cases. Most of these cases had involvement of the facial nerve. He noted that the disease was unaccompanied by cerebral and mental symptoms even in terminus. He reported that the cerebrospinal fluid was normal in all instances. This group had a mortality rate of 26.6 per cent. In the same paper Bashford discussed the morbid anatomy of the disease in man and monkey and the experimental production of the disease in the monkey. He thought that he was able to transmit the disease to monkeys, and from monkey to monkey by subdural inoculation of glycerine emulsions of the affected spinal cord. The pathology in the monkey was similar to that in man. Wilson thought that he was able to culture the organism from the spinal cords of the cases described by Bradford and Bashford and with it produce the disease in monkeys. He thought that the organism that he recovered was a virus. The etiological factor of Bradford, Bashford, and Wilson was never confirmed and Arkwright (1919) disproved their work and showed that the globoid bodies which they demonstrated were contaminants. In a note appended to Arkwright's paper they retracted their previous claims.

Foster Kennedy (1919) re-introduced the term 'neuritis' in a description of four cases. Casamajor (1919) suggested the name of acute infective meningomyeloneuritis and he noted that the cerebrospinal fluid was normal in his cases.

opinion of some that there are no changes of note in the latter. Certain pathological changes in the viscera are of interest and importance. The search for an infecting agent will be briefly noted, and thoughts on the nature of the disease will be presented.

During and immediately following the War of 1914-1918, cases of polyneuritis, occurring endemically, were described under various titles by many authors including Holmes (1917), Bradford, Bashford and Wilson (1918), Casamajor (1919), and Kennedy (1919). Sporadic reports have since appeared in the literature and with them further confusion has arisen as to the unity of the clinical and pathological pictures presented.

As a basis for the present clinical description, sixteen cases (Table 1) have been selected from those studied at the Cincinnati General Hospital within the last five years. In this group of cases, as in those in the literature, the diagnostic cognomen was as varied as the number of patients. The appellations applied have included all the synonyms listed above and in addition such terms as acute infectious febrile polyneuritis, encephalitis, post-measles or chickenpox encephalomyelitis, ascending myelitis, and simply polyneuritis. There is no doubt that had a comprehensive search of the hospital files been made many cases could have been found, each under a different heading. In the light of the multiplicity of terms one would not know that there has been an increased recognition of the disease in latter years. Brown (1938) pointed out that "infectious polyneuritis" is second in frequency only to alcoholic polyneuritis in North America.

#### BRIEF REVIEW OF THE CLINICAL LITERATURE

For a comprehensive review of the literature covering the subject, one may consult the papers of Guillain (1936), Gilpin, Moersch and Kernohan (1936), Hecht (1937), and the review of the entire subject of neuritis by Collier (1932). Osler (1892) lucidly described the disease under the name of acute febrile polyneuritis, and noted the difficulty of its differentiation from Landry's paralysis. Mills (1898) in a paper entitled "The reclassification of some organic nervous diseases on the basis of the neurone" first introduced the term *neuritis*, a name which has recurred frequently in the literature. Patrick (1916) reported two cases of facial diplegia in multiple neuritis, thereby

focusing attention on the possibility of the involvement of the seventh nerve in this disease. Guillain, Barré and Strohl (1916) were the first to note the high protein and low cellular content of the cerebrospinal fluid ("albumino-cytologic dissociation") in this disease. They also stated that the prognosis of the disease was favorable. In fact, Guillain (1936) separated his cases from those having a fatal result preferring to believe that they were afflicted with a distinct morbid process. Since 1916 the syndrome has been known in France under the modest and comparatively innocuous term of the "Guillain-Barré Syndrome." Under the heading of "acute febrile polyneuritis," Gordon Holmes (1917) discussed the clinical course of twelve patients and presented a pathological study in two of them. A most comprehensive and illuminating work on the subject is the monograph by Bradford, Bashford and Wilson (1918). Bradford clearly described the clinical phenomena in thirty cases. Most of these cases had involvement of the facial nerve. He noted that the disease was unaccompanied by cerebral and mental symptoms even in terminus. He reported that the cerebrospinal fluid was normal in all instances. This group had a mortality rate of 26.6 per cent. In the same paper Bashford discussed the morbid anatomy of the disease in man and monkey and the experimental production of the disease in the monkey. He thought that he was able to transmit the disease to monkeys, and from monkey to monkey by subdural inoculation of glycerine emulsions of the affected spinal cord. The pathology in the monkey was similar to that in man. Wilson thought that he was able to culture the organism from the spinal cords of the cases described by Bradford and Bashford, and with it produce the disease in monkeys. He thought that the organism that he recovered was a virus. The etiological factor of Bradford, Bashford, and Wilson was never confirmed and Arkwright (1919) disproved their work and showed that the globoid bodies which they demonstrated were contaminants. In a note appended to Arkwright's paper, they retracted their previous claims.

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Viets (1927) under a heading of "Acute polyneuritis with facial diplegia" recorded two cases and described the morbid anatomy in one. He noted the "albumino-cytologic dissociation" in the cerebrospinal fluid. Collens and Rabinowitz (1928) reported a case of polyneuritis with facial diplegia which occurred three weeks after the onset of mumps, and in which the cerebrospinal fluid had a high protein content without cells. These writers found four similar cases in the literature. Urquhart (1934) reported a case of "infectious polyneuritis" which followed the onset of measles by one week. These latter reports, coupled with the close association of the disease to upper respiratory and grippal infections seemed to give credence to the idea held by many that "infectious polyneuritis" was a virus disease. Cobb and Coggeshall (1934) in their review of neuritis pointed out that the cerebrospinal fluid may be normal or may contain increased protein with a few cells. Merritt and Fremont-Smith (1938) have analyzed the cerebrospinal fluid of thirty patients suffering from "infectious polyneuritis". The cell count was normal in 80 per cent of their cases. In one case there were 175 white blood cells per cubic millimeter in the cerebrospinal fluid, and in the remainder there were less than 30 cells per cubic millimeter. In eight of their thirty patients the protein content of the cerebrospinal fluid was normal.

Hecht (1937) clearly described the disease as it occurs in children.

#### CLINICAL DESCRIPTION

The seasonal incidence of "infectious polyneuritis" seems to be of minor importance but it is worth noting that most cases tend to appear in the winter and autumn (thirteen of sixteen cases in our series). The distribution between the sexes is about equal, and there is a tendency towards equal distribution in the various decades of life.

The mode of onset of this disease seems rather constant. There is, as a rule, a history of some previous recent infection, usually a cold or grippé. This was true in twelve of our sixteen patients. In one patient the disease manifested itself 11 days after the onset of measles and two others 15 and 20 days respectively following the onset of varicella. A fourth patient demonstrated the polyneuritic symptoms during convalescence from pneumonia. Accompanying the

mild upper respiratory prodromata the patient usually noted vague generalized aches and pain in the calves of the legs and in the back. The initial symptoms usually are not severe enough to cause the patient to go to bed. The recovery from the infection frequently is complete and there may be a latent period of days to months usually one to three weeks, before the neuritis becomes manifest. Headache has occurred with sufficient frequency (in our series of ten of sixteen cases) to be of some significance in the consideration of the prodromata.

In our experience the most common initial symptom is referable to the sensory system. Pain in the back, and in the calves of the legs is frequent and is usually described by the patient as rheumatism or lumbago. The initial complaint of paresthesiae usually numbness in hands and feet, is not infrequent. Pain is at times so severe that it may require heavy sedation and mask for a while the progressive motor disability. An unique initial symptom elicited from one patient (a physician) was a sensation of tingling of the tip of the tongue and tenderness of both masseter muscles. Although the subsequent weakness is of the proximal type the sensory disturbance is usually limited to the distal portions of the extremities. By the time the patient reaches the physician, objective sensory signs usually can be elicited. In eleven of our patients the appreciation of vibration was impaired, and in three of the remaining five a note of this examination was not made. Pain and light touch may be diminished. The sensory disturbances diminish in severity in a proximal manner. At no time do the sensory phenomena appear to be as profound as the motor weakness. Muscle and nerve tenderness is present in patients

<sup>4</sup> In a recent patient (case 14) the sensory phenomena were most striking and completely overshadowed the motor disturbances, which were of typical distribution and included racial diplegia. For five days after onset of the disease, the patient demonstrated a glove and stocking type of impairment to pain, temperature, light touch, position, and vibration stimuli. Two days later he was unable to smell ground coffee or cural in either nostril. There was complete anesthesia to pinprick of the entire tongue and circumoral region, and taste was not appreciated in the anterior two-thirds of the tongue. Within five days after admission the sensory signs began to clear in the extremities and tongue, and taste and smell was again appreciated slightly. On the ninth day after admission there occurred severe paresthesiae and loss of pain sense on one side of the face and paroxysmal tinnitus and deafness in the ear of the same side. The corneal reflex on this side was depressed. Three weeks after admission and four weeks following onset of the disease all of the sensory phenomena had disappeared except a small, patchy area of anesthesia on the outer aspect of one thigh.

with "infectious polyneuritis" practically without exception. Hyperesthesia is sometimes so severe that the pressure of the bed clothes may be obnoxious.

The period between the onset of sensory disturbances and of motor disability may vary from a few hours to several days, or even a week or more. In this interim the patient may attempt to fight off the disease or he may go to bed. The onset of motor signs may be catastrophic. Thus a dentist, who for several days previously had noted mild but progressive weakness and clumsiness of his hands in the performance of surgical procedures, suddenly collapsed while crossing a street and was unable to rise. This type of onset is unusual, but the progress of the disease once it has begun is quite rapid. The motor signs can be briefly summarized by stating that they tend to be symmetrical and bilateral, are progressive, and almost invariably are more severe in the proximal than in the distal musculature. The affected limbs are flaccid. The usual history is that the quadriplegia developed over a period of several days, although infrequently weeks may be required, and periods of remission may occur rarely. Weakness occurs most commonly in the lower extremities and gradually spreads to involve the musculature of the upper limbs and of the trunk. The paresis progresses as one observes the patient. An individual when first seen may complain only of weakness and difficulty in walking. Examination may reveal moderate weakness of the lower extremities with slight motor impairment in the upper extremities. Then the patient may rapidly run the entire gamut of signs and symptoms of the morbid process. He successively finds himself unable to lift the lower extremities from the bed, has difficulty in rising to the sitting posture, following which progressive impairment in the use of the upper limbs may be noted. The picture presented at its worst is that of a helpless individual unable to turn over in bed, elevate his head, feed himself, or carry out other bodily needs. The only voluntary motion retained may be slight "wriggling" movements of the toes and fingers. In other cases the paresis may be mild, and when it is seen in individuals who are well nourished and appear to be healthy, the disease may be thought to be of neurasthenic origin. One of our patients, a robust, plethoric, obese 46 year old female walked into the Receiving Ward complaining of burning and crawling sensation in the hands and feet and weakness of all extremities. The impression of the physician who

examined her was that she was suffering from psychoneurosis and questioning revealed a history which was deemed to be compatible with that diagnosis. Within 24 hours this patient developed flaccid quadriplegia which was almost complete, and which was accompanied by facial diplegia, aphonia and respiratory distress. On the second day she died in a respirator. A muscularly well developed man was observed over a period of two years in various departments of the hospital and a diagnosis of psychopathic personality made. He was termed a malingerer who did not wish to work, and who was obsessed with the idea of his muscular weakness. However, after two years of intermittent observation a careful neurological examination and an analysis of the cerebrospinal fluid revealed the true nature of his condition. During this two year period the patient had made several attempts at suicide, due in a great measure to the unsympathetic attitude of his physicians.

The involvement of the trunk and abdominal musculature increases the seriousness of the outlook. Intercostal disability causes the patient to rely solely upon the diaphragm for respiration and if the disease extends to involve the latter the prognosis is indeed poor. It has been the experience of many that if it is found to resort to artificial respiration (usually by use of the Drinker apparatus) death is imminent. Of the five cases of our group necessitating the use of a respirator two survived. One was a child and it is generally agreed that the prognosis in children is almost invariably good. The other patient was a young adult, aged 22, who was placed in the respirator prophylactically, so to speak, while he still had fair respiratory excursions.

Weakness is found in whole segments of a limb rather than muscle groups and one limb may be involved more than its fellow of the opposite side. Wasting other than that due to disuse is not a prominent feature. Fibrillations were seen in the arms, calves and thighs of one of our patients. This man had moderate contracture of the gastrocnemius muscle two years after onset of the illness which resulted in minimal disability in walking.

All tendon reflexes are diminished or unobtainable. The abdominal reflexes are infrequently affected. The plantar responses are either not elicited or are flexor in type. No other abnormal reflexes are noted.

The facial nerves usually are involved. The facial paresis may be

bilateral or unilateral, and may precede or succeed the weakness of the extremities and trunk. It has been missed in some patients because of its bilaterality. Of the 20 cases recorded by Bradford, Bashford, and Wilson, 14 had bilateral and 3 unilateral involvement of the face. In our 16 patients, 10 have bilateral and 3 unilateral facial paresis. The paresis is present in varying degrees of severity from case to case, and is of the nuclear or infranuclear type, involving the brow and eyelids as well as the lower portion of the face. Early in the course of the disease, it is not usually of such severity as that found in the ordinary case of Bell's palsy.

Besides the affection of the seventh nerve, involvement of other cranial nerves has been observed and was prominent in our group. We have seen involvement of all the cranial nerves in our series of patients.<sup>5</sup> Four of our patients demonstrated paralysis of accommodation. This is of interest since it has been held by many observers (Grinker (1937), Price (1937)) that paralysis of the ciliary muscle is pathognomonic of the polyneuritis of diphtheria. We are inclined to believe that this phenomenon may occur in either condition, but that it is more frequent in diphtheria. Palatal weakness of varying degrees occurred in eight patients and dysphagia in six. A hoarse or nasal quality to the voice was noted in nine. The vocal cords were examined in two patients and were immobile in the cadaveric portion. Seven individuals had weakness of the muscles of mastication, four had soreness on pressure over the masseter muscles and four had diminution of sensation in the distribution of the fifth nerve. One patient (case 14) demonstrated anosmia, deafness, tinnitus, vertigo, and loss of the sense of taste. Paresis and fibrillation of the tongue have been reported by Bradford, Bashford and Wilson. Gilpin, Moersch and Kernohan noted choked discs in three of their patients, and this may be correlated with our observation that these patients tend to have a high normal or slightly elevated cerebrospinal fluid pressure. We have seen optic neuritis in two cases.

The vesical and rectal sphincters are rarely involved except in children or in the moribund. Constipation is common and probably is due to the weakness of the abdominal musculature.

<sup>5</sup> In a recent example of the disease a patient exhibited total external ophthalmoplegia with exophthalmus, from which a rather prompt and complete recovery was made.



Mild depression or delirium have been noted in several patients in our series particularly in those who have been conspicuously paralyzed. In one instance a patient rather severely depressed but otherwise clear demanded to be taken from a respirator, despite the realization that he could not breathe outside of it.

Fever in the absence of complications such as pneumonia is not common and when present is usually seen in the first week of the illness and rarely exceeds 102°F. Among our three patients who died two had a terminal rectal temperature of 102°F and in the other it was normal. Even in the absence of fever most patients have a mild tachycardia varying from 70 to 100 per minute. Higher pulse rates are exhibited by those with pyrexia and in those in which the outcome is rapidly fatal.

The cerebrospinal fluid findings have long been a moot point. The presence of a high total protein content with few or no cellular elements is deemed to be an invariable diagnostic feature by the French writers. Some of the earlier writers pointed out that the cerebrospinal fluid was always normal. However the cerebrospinal fluid examinations were hardly complete in some instances and in others it is not stated clearly what constituted the examination. Where the test has been quantitatively performed it is found that the total protein usually varies between 80 and 800 mg per cent. The range in our group was from 70 to 400 mg per cent with an average of 172. The protein content of the cerebrospinal fluid tends to increase in the acute phase of the disease. An elevation in the protein content of the cerebrospinal fluid may be found as long as three years after the onset (case 11) particularly in those cases where recovery has been delayed. We have seen a patient recently, who has been followed by a neurologist for five years and in whom the cerebrospinal fluid protein has been elevated since the onset of the disease. This patient has not made a satisfactory clinical recovery. The number of white blood cells in the cerebrospinal fluid in our series varied from 0 to 26 usually all lymphocytes. Our cases usually had high normal or slightly increased cerebrospinal fluid pressures varying from 150 to 220 mm of water. There was one mid zone and one first zone colloidal gold curve in our group. It should be noted that the revelation of the typical cerebrospinal fluid abnormalities in infectious polyneuritis may depend on

more than one spinal tap and analysis of the fluid Stone and Aldrich (1940) have recently reported two cases in which the cerebrospinal fluid protein was initially rather low (46 and 67 mg per cent) for "infectious polyneuritis," but during the course of the disease the protein reached high values (375 mg per cent)

The urine may contain small amounts of albumin during the acute phase A slight blood leucocytosis, varying from 10,000 to 13,000 cells per cubic millimeter was found in four patients, and in one instance there were 23,000 white blood cells per cubic millimeter during the first weeks of the illness However, the blood picture is usually within normal limits

The duration of the disease is an inconstant factor The acute phase of the malady may last from two weeks to four months The duration of illness in our series has been from eight weeks to three years, and in the latter instance the patient is not yet well The major portion of the time is consumed in slow convalescence Some of these patients never seem to regain their former vigor Occasionally the patient whose disease is considered to be stationary may experience a sudden and rapid progression In the fatal case death usually occurs within two weeks after the onset of the initial symptom, and is considered to be due to respiratory failure The mortality rate varies from 14 per cent in the series reported by Gilpin, Moersch and Kernohan to 42 per cent in Forster, Brown, and Merritt's series Guillain, Barré, and Strohl (1916) and Guillain (1936) postulated that the mortality must be nil to be compatible with the syndrome that they have described It is most likely that they were dealing with a benign form of the disease The mortality in our group was 18.8 per cent In the 26 patients with "infectious polyneuritis" described by Forster, Brown and Merritt (1941) the mortality was 42 per cent They observed eight deaths in ten patients between the years 1938 to 1940, whereas previous to 1938 only three of sixteen patients had died as the result of the disease They believe that their experience indicates an increase in virulence of the disease in late years

Recovery is usually complete and no recurrences have been reported Some patients may have residual minor weakness Improvement is usually slow and recovery of function occurs in the same order in which it was lost The last sign to remain may be a moderate weakness of one side of the face

Two diseases which need to be considered in the differential diagnosis are diphtheritic polyneuritis and poliomyelitis. In the former, the history of contact and a brief period of incubation, the presence of the virulent organisms in cultures taken from the nose and throat, and the history or presence of a membrane are helpful. Differentiation by means of the clinical picture is difficult and, at times, well nigh impossible, since in both diphtheritic and infectious polyneuritis the paresis, sensory signs, cranial nerve involvement and spinal fluid findings may all be quite similar. In cases in which the diagnosis of "infectious polyneuritis" is made, care should be taken to rule out diphtheria by the use of nose and throat cultures and the Schick test. Poliomyelitis may sometimes be considered in the differential diagnosis, but the presence of cells in the cerebrospinal fluid early in the disease aids in diagnosis. The absence of objective sensory signs in poliomyelitis also is helpful. Poliomyelitic paralysis tends to limit itself to muscle groups while the paralysis of infectious polyneuritis is widespread and symmetrical in the extremities. Poliomyelitis occurs in epidemics, mainly in the summer months. Tumors of the spinal cord and syringomyelia need at times to be considered, but careful clinical and cerebrospinal fluid studies will usually make the diagnosis clear. The differentiation of neuritis due to other better known causes is, of course, the chief consideration in the differential diagnosis.

In summary, the clinical picture of "infectious polyneuritis" is rather characteristic. The onset usually follows (days or weeks) a mild upper respiratory infection. The initial nervous symptoms commonly are referable to the sensory system. There follows closely the progressive, bilaterally symmetrical, flaccid quadruplegia which is predominantly proximal. The sensory signs are overshadowed by the motor phenomena. There is a high incidence of involvement of the facial nerve. Involvement of other cranial nerves may be manifested by blurring of vision (jumbling of the printed page), palatal paralysis, dysphagia, nasal or hoarse voice, and, at times, by involvement of the muscles of mastication. The cerebrospinal fluid early in the disease typically shows a high protein content with little or no cellular increase. The mortality is high, varying from 14 to 42 per cent. Convalescence is slow, but recovery usually is complete. It should be noted that once improvement begins, it usually continues at a rapid rate until a stage is reached when there are a few residual

signs, such as mild generalized weakness, or weakness of one side of the face

The therapy of the disease is, as yet, symptomatic. Treatment in the early phases should be directed towards the alleviation of pain and measures directed toward the well-being of the patient. The appearance of bulbar signs must be watched for carefully. Assurance and encouragement is not amiss, especially in those patients with incipient or well developed respiratory difficulties. Mucous should be aspirated from the throat and trachea and an access to a respirator (preferably of the Drinker type) should be assured. These individuals are frequently unable to feed themselves or to swallow, and careful regulation of nutrition is needed. They should receive a nutritious, high vitamin diet. We have administered vitamin B<sub>1</sub> (intravenously in the form of thiamin chloride) in large doses (50 to 100 mg daily) to nine patients in some cases as long as three weeks. One patient received 2050 mg of this vitamin intravenously. The only effect noted was the relief of disturbing sensory symptoms, such as pain and paresthesiae, in six subjects. There was no change in the motor status of any of them.<sup>6</sup> After the acute stage of the disease has passed physiotherapeutic measures such as regulated passive and active exercises and massage should be carried out. Protective splints should be used to prevent the stretching of weakened muscles.

In the light of recent investigations on the shortening of the duration of lower motor neurone paralysis by Wolf (1940), prostigmin should most certainly be tried in "infectious polyneuritis."

#### REVIEW OF THE LITERATURE ON THE PATHOLOGY OF THE DISEASE

In an incomplete pathological survey of the central and peripheral nervous systems, Holmes (1917) noted little or no change in the peripheral nerves and their roots. Swelling of the neurones of the ventral horns of the spinal cord with chromatolysis and eccentricity

<sup>6</sup> In two recent cases we have administered vitamin E in the form of wheat germ oil (45 minims daily). In one case this drug had no effect on the severe sensory manifestations. However within three weeks after admission to the hospital, and four weeks after onset of the illness, the patient was able to walk about, although the initial motor signs were severe. In the other case the patient was able to sit up in a chair within two weeks after removal from a Drinker respirator. Use of this vitamin in other patients is necessary before any conclusions can be drawn concerning its efficacy in this disease.

of the nuclei and chromatolysis of the Betz cells were recorded. These findings he believed indicated that the disease was a form of peripheral neuritis and excluded any widespread affection of the nervous system. Bradiord, Bashford and Wilson (1918) pointed out (1) the acute neuritis of the sciatic nerve (2) spotty involvement of all the cell columns of the spinal cord with perineuronal (not perivascular) round cell infiltration (3) ependymal proliferation (4) changes in the cells of the posterior root ganglia in the lumbar and dorsal regions (5) round cell infiltration about the neurones in the deeper layers of the cortex with very little neuronal change and (6) spotty degeneration of muscles. Bradiord also recorded slight and variable infiltration of round cells in the portal tracts of the liver. The kidneys in his cases showed early patchy parenchymatous and glomerular nephritis. Casamajor (1919) reported the pathology of the spinal cord in two cases. His findings in the main revealed (1) hyperemia, hemorrhage, edema and fibrous swelling of the arachnoid of the cord with thickened pia mater (2) increased neuroglia nuclei in the central gray matter of the cord around the nerve roots and posterior root ganglia (3) evidence of beginning degeneration of both a secondary and primary character in the anterior horn cells with hyperemia of the gray matter (4) marked degeneration of a primary and secondary character of the nerve fibers (5) marked degeneration of the posterior root ganglion cells with neuronophagia. He pointed out that the round cell infiltration described by Bradiord, Bashford and Wilson was composed of glial elements. Viets (1927) found slight changes in the facial nuclei with mild changes in the nerve cells of the spinal cord mainly confined to the lumbar region. Greenfield and Carmichael (1935) examined the terminal portion of the internal branch of the anterior tibial nerve of one patient by the osmic acid method. They noted severe degenerative changes in this nerve. Of the three cases reported by Gilpin, Moersch and Kernohan (1936) no note is made as to the examination of the central nervous system in one and in another Hodgkin's disease was a complicating factor. The essential changes found in the third case were degeneration of the nerves and some changes in the posterior root ganglia and the pontine nuclei. The brain stem, cerebellum, basal nuclei and cerebrum were normal. Honeyman (1937) reported on the pathology of four cases

signs, such as mild generalized weakness, or weakness of one side of the face

The therapy of the disease is, as yet, symptomatic. Treatment in the early phases should be directed towards the alleviation of pain and measures directed toward the well-being of the patient. The appearance of bulbar signs must be watched for carefully. Assurance and encouragement is not amiss, especially in those patients with incipient or well developed respiratory difficulties. Mucous should be aspirated from the throat and trachea and an access to a respirator (preferably of the Drinker type) should be assured. These individuals are frequently unable to feed themselves or to swallow, and careful regulation of nutrition is needed. They should receive a nutritious, high vitamin diet. We have administered vitamin B<sub>1</sub> (intravenously in the form of thiamin chloride) in large doses (50 to 100 mg daily) to nine patients in some cases as long as three weeks. One patient received 2050 mg of this vitamin intravenously. The only effect noted was the relief of disturbing sensory symptoms, such as pain and paresthesiae, in six subjects. There was no change in the motor status of any of them.<sup>6</sup> After the acute stage of the disease has passed physiotherapeutic measures such as regulated passive and active exercises and massage should be carried out. Protective splints should be used to prevent the stretching of weakened muscles.

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present in equal severity throughout the peripheral nervous system. Edema was evidenced by the wide separation of the perineurium from the funiculi and by the appearance of fairly wide clefts in the substance of the bundles. The vessels of the spinal roots were congested and in one case were surrounded by small hemorrhages. There was little or no thickening of the vascular endothelium. Most of the nerve roots of the spinal cord contained an increase in cellular elements. This was most marked in the thoracic region although the cellular proliferation was obvious in other areas. In certain instances this cellular increase tended to be spotty with areas of focal accumulation of cells. The hypertrophied sheath of Schwann cells were in predominance. However groups of phagocytes usually containing ingested cellular debris were seen not infrequently. In one case they were prominent in number and size and resembled "foam cells".

An occasional lymphocyte was found but there was no perivascular round cell cuffing in the nerves. Polymorphonuclear leukocytes were conspicuously absent. There were no inflammatory cells in the interstitial tissue of the nerve bundles but there was a slight increase in the density of the connective tissue. The myelin sheaths of the spinal roots appeared swollen, fragmented and moderately decreased in number. The most striking changes in the spinal roots were found in the axis cylinders and were well demonstrated by the use of the Bodian one per cent protargol method (Fig. 1). Marked swelling and beading of the cylinders was a prominent feature so that, at times, the nodules were many times the diameter of the normal axis cylinders. Not infrequently there was slight to marked fragmentation of the axones with a tendency to corkscrew formation. Some axones were wavy, other were broken up and curled into small balls. These findings were interpreted as evidence of active degeneration. In some regions the axis cylinders were markedly decreased in number.

(b) *Cauda equina*. The nerves of the cauda equina were similarly affected where edema, cellular proliferation (mainly hypertrophied neurilemma cells), congestion and axonal and myelin sheath degeneration were the most notable features. Phagocytes were found in small numbers and their tendency to accumulate in foci was noted again. Lymphocytes and other inflammatory cells were rarely seen and there was no perivascular infiltration.

(c) *Peripheral nerves*. Less than 50 per cent of the myelin sheaths

and came to the conclusion that "in none were significant changes found in the peripheral and central nervous systems."

#### PATHOLOGY OF THE NERVOUS SYSTEM

Our three fatal cases had many features in common from the standpoint of morbid anatomy. Autopsies were performed four hours after death in two cases and six hours after death in the third. In one case the entire brain, spinal cord, and portions of the peripheral nervous system were placed in a dilute solution of formaldehyde, U.S.P. (1:10) and sectioned six days later. In the other two cases representative sections of the unfixed nervous system were placed in the following fixatives: ten per cent formalin, one per cent fresh osmic acid (nerves), and seventy per cent alcohol. The staining techniques used were hematoxylin and eosin, eosin methylene blue, cresyl violet, Bodian (one per cent protargol), scarlet red, one per cent fresh osmic acid, the oligodendroglia silver carbonate stain of Hortega, and the Smith-Quigley stain for myelin sheaths.

*Macroscopic findings.* The only abnormal features on gross examination of the brain, spinal cord and peripheral nerves were a moderate degree of edema of the brain and slight vascular congestion of the overlying leptomeninges of the brain and spinal cord. In addition slight herniation of the uncus of the temporal lobe was present in all. On sectioning the brain and spinal cord nothing remarkable was observed. There was slight congestion of the vessels. There was no bulging of the spinal cord on section, as may be usually seen in acute anterior poliomyelitis.

*Microscopic findings.* **Nerves.** The peripheral nerves revealed fairly uniform changes. Sections taken from the cauda equina, the brachial plexus, the genitofemoral, external peroneal and sural nerves and from the emergent dorsal and ventral spinal roots and cranial nerves were stained by the hematoxylin and eosin, cresyl violet, Bodian, osmic acid and Hortega silver carbonate methods. In brief, the abnormalities were (1) marked edema of the nerve bundles, (2) congestion, (3) moderate increase in cellularity with a tendency to focal accumulation of cells, (4) swelling and beading of the myelin sheaths, (5) swelling, beading, corkscrew formation and fragmentation and dissolution of the axis cylinders.

(a) **Spinal roots.** The edema in the spinal roots was obvious and was



present in equal severity throughout the peripheral nervous system. Edema was evidenced by the wide separation of the perineurium from the funiculi and by the appearance of fairly wide clefts in the substance of the bundles. The vessels of the spinal roots were congested and in one case were surrounded by small hemorrhages. There was little or no thickening of the vascular endothelium. Most of the nerve roots of the spinal cord contained an increase in cellular elements. This was most marked in the thoracic region although the cellular proliferation was obvious in other areas. In certain instances this cellular increase tended to be spotty with areas of local accumulation of cells. The hypertrophied sheath of Schwann cells were in predominance. However groups of phagocytes usually containing ingested cellular debris were seen not infrequently. In one case they were prominent in number and size and resembled 'foam cells'.

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(b) *Cauda equina*. The nerves of the cauda equina were similarly affected where edema, cellular proliferation (mainly hypertrophied neurilemma cells), congestion and axonal and myelin sheath degeneration were the most notable features. Phagocytes were found in small numbers and their tendency to accumulate in foci was noted again. Lymphocytes and other inflammatory cells were rarely seen and there was no perivascular infiltration.

(c) *Peripheral nerves*. Less than 50 per cent of the myelin sheaths

of the smaller funiculi of the external peroneal and sural nerves took the fresh osmic stain. There was an average of 2500 myelin sheaths per square millimeter of nerve, as counted from photomicrographs of the osmic acid preparations (the number of myelin sheaths in a normal nerve range between 5000 and 10,000 per square millimeter). The stained sheaths were mainly large and medium sized. However, they



FIG. 1. THE FIFTH THORACIC POSTERIOR ROOT AS IT ENTERS THE SPINAL CORD, CASE 3

Fragmented axones of irregular diameter some demonstrating marked beading are illustrated. Bodian protargol stain.  $\times 200$

were not normal as the rings of myelin (on cross section) were not smooth and contained debris in the center. The smaller sheaths rarely took the stain, probably indicating their deviation from normal. In the larger funiculi a greater number of myelin sheaths showed affinity for the osmic acid (about 50 to 75 per cent) but again the smaller sheaths were few in number. The myelin sheaths examined

in longitudinal section were markedly swollen and beaded undergoing dissolution. No normal axones were seen in the peripheral nerves stained by the modified silver impregnation method. The axones were swollen to many times their normal size and beading was a notable feature (Fig. 2). Many were undergoing fragmentation and many fibers were divided into small filaments. Corkscrew formation of the axis cylinders was common. Increase of the cellular elements was demonstrable by this silver method and consisted mainly

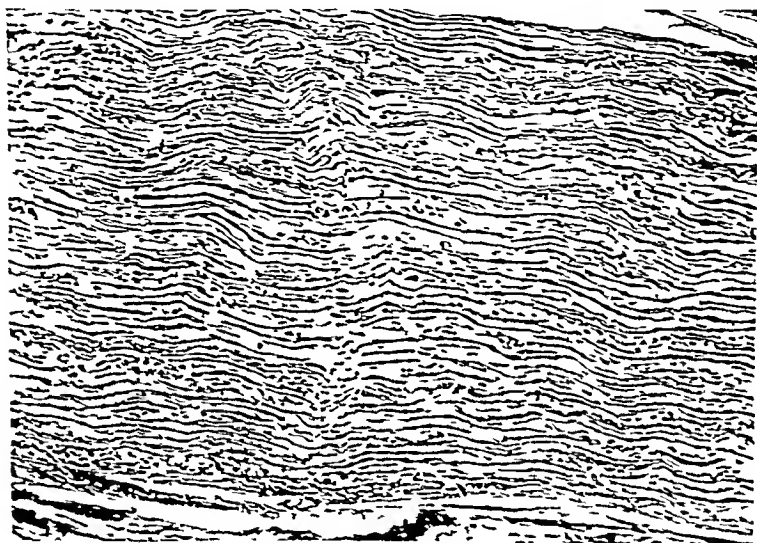


FIG. 2. A SECTION FROM THE PERONEAL NERVE OF CASE 2.

Note the swollen axones and the increase of cellular elements. Bodian protargol stain.  $\times 200$ .

of hypertrophied sheath of Schwann cells. There was a slight generalized infiltration of phagocytes and lymphocytes, most prominent in the peroneal nerves. In the latter nerve an occasional perivascular round cell infiltration of lymphocytes and a few phagocytes were found. Similar changes were demonstrated in nerves from the brachial plexus and in the genitofemoral nerves.

**Ganglia.** Sections from the Gasserian ganglia (Fig. 3) and from the dorsal root ganglia taken from various thoracic levels showed many changes. The ganglia appeared edematous. The nerve cells were

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active myelin sheath and axis cylinder degeneration. In neither the ganglia nor their attached nerve bundles were any polymorphonuclear leukocytes seen.

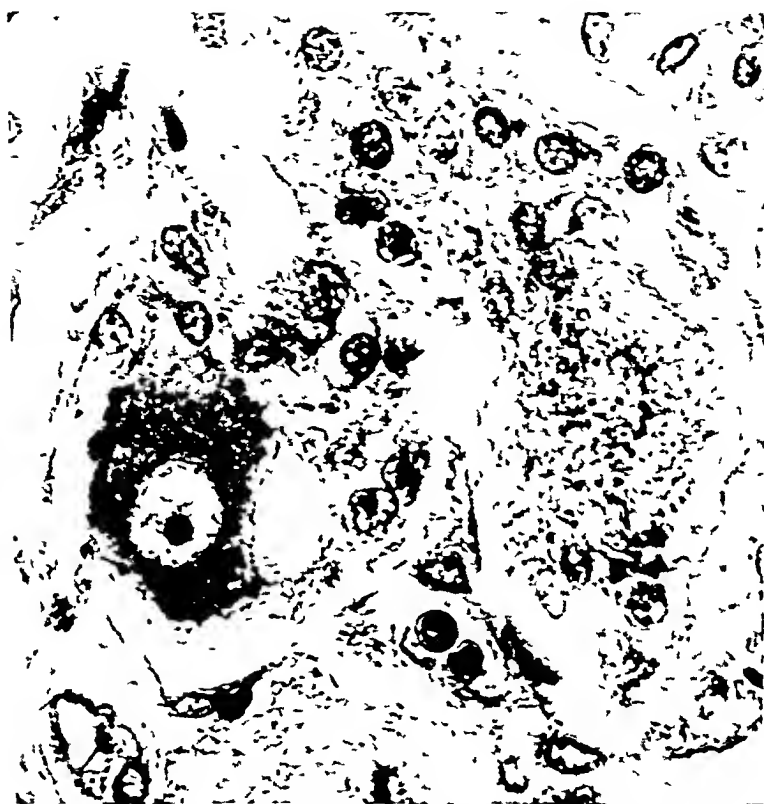


FIG. 4. CELLS IN THE ABDOMINAL SYMPATHETIC GANGLIA (CASE 1)

An unaffected nerve cell adjacent to a nerve cell that is completely vacuolated. Small rounded bodies which are acidophilic are visible in the remains of the latter cell. Eosin methylene blue  $\times 10,000$ .

Degenerative changes were found in some of the nerve cells in the abdominal sympathetic ganglia. These consisted of vacuolization and the appearance of acidophilic granules in the cytoplasm of some of the nerve cells (Fig. 4).

**Spinal Cord.** Sections taken from representative levels of the spinal

slightly to moderately reduced in number and tended to stain homogeneously with concentration of tigroid material about the periphery. Nuclei were absent in 25 to 50 per cent of the cells (sections cut at  $4\mu$ ) and many of those present were in aberrant positions. The ganglion cells were reduced in size and had well defined capsular spaces. There was proliferation of capsular cells and some ganglion cells were surrounded by satellite glial nuclei or were undergoing neuronophagia. Several "shadow" cells were seen and some ganglion cells contained

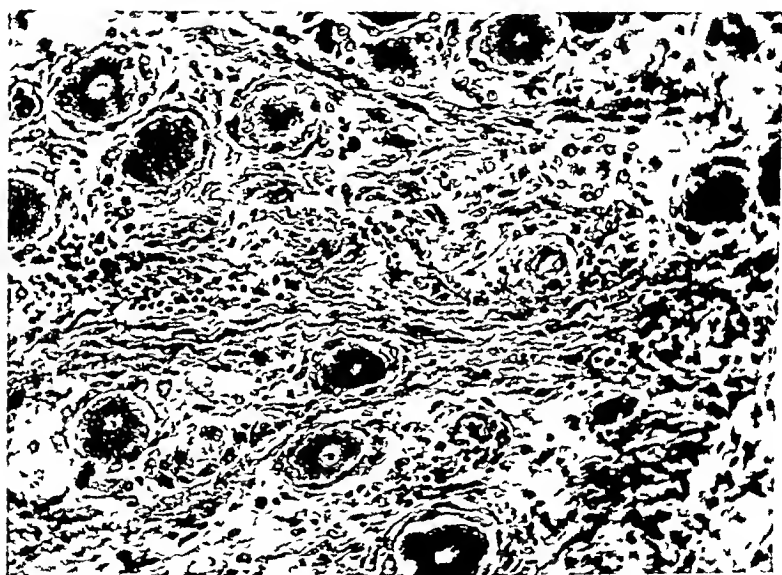


FIG. 3. A SECTION FROM THE GASSERIAN GANGLION OF CASE 1.

Note the interstitial infiltration with mononuclear cells and homogeneous staining of nerve cells. Eosin methylene blue  $\times 500$ .

large collections of fat, or were vacuolated. The cells in the interstitial tissue were increased in number, and there were focal accumulations of these cells in which an occasional phagocyte with ingested debris was seen. Silver impregnation revealed beading, fragmentation, swelling and "corkscrew" formation of the axones of the ganglia, the same change that was noted in the peripheral nerves. The striking findings in these nerve bundles as in the others examined were edema, increased cellularity, the presence of phagocytes and lymphocytes, and

(ghost cells) The changes were equally marked in the various cellular groups of the anterior horns. In the ventral horns of one case several binucleated nerve cells were seen.

A feature of the nuclei dorsalis (Clarke's columns) was the patchy outfall of nerve cells. The cells of the lateral gray columns were decreased in number. In the dorsal horns the cells usually stained pale and diffusely and demonstrated hypochromatic nuclei composing the bulk of the small shrunken cells.

There was a slight increase in glial elements mainly oligodendroglia in the gray matter of the cord. Satellitosis and neuronophagia were seen only occasionally and the rarity of these reactions was noteworthy. The vessels of the gray substance were moderately congested. There was no change in the vessel walls. However in one case there were many small perivascular hemorrhages which in the spinal cord were confined in the main to the ventral horns and to the area surrounding the central canal. About these foci there was no evidence of any inflammatory reaction. In this case there were many neurones of the anterior horns which contained ingested blood pigment which appeared black in the cresyl violet preparations.

Throughout the cord there was slight but nevertheless definite increase in ependymal cells surrounding the central canal. Abnormalities noted in the white matter were irregularity in the diameter of the myelin sheaths, mild and diffuse loss of myelin sheaths, swelling and irregularity in size of the axones seen in cross section and some axonal loss. There were large numbers of corpora amylacea diffusely scattered throughout the white and gray matter.

**Brain Stem.** The brain stem showed changes which were somewhat similar to those noted in the spinal cord. The morbid process appeared to be a diffuse one with some tendency to involve certain nuclear structures and nerves more severely. The hypoglossal nucleus contained the least pathology. The most striking changes were noted in the olivary nuclei where the nerve cells were stained diffusely and contained much fatty pigment which at times composed the bulk of the cell. Ghost cells were present in large numbers and many neurones of the olivary nuclei contained clear vacuolar inclusions. Wavy cell processes were occasionally noted. The cells of the tractus solitarius and of the nucleus ambiguus and dorsal motor

cord demonstrated some involvement of the cells of the gray columns in all cases. The changes were most marked in the cervical and thoracic cord although lower levels showed some neuronal damage. The ventral gray columns throughout the spinal cord were most notably affected. Here the number of neurones was decreased at many levels and some of the nerve cells appeared small and shrunken. Not infrequently bizarre shaped anterior horn cells with wavy processes were seen. The perineuronal spaces were widened. A number of the neurones, notably the smaller ones were stained diffusely and

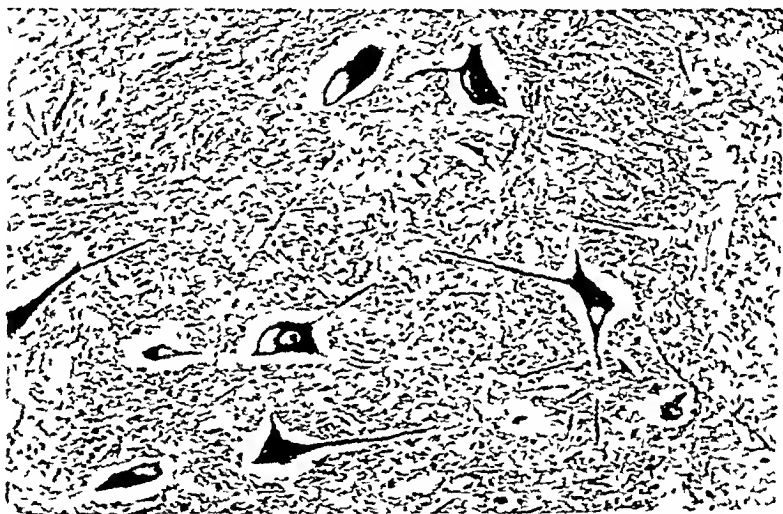


FIG. 5. VACUOLES IN THE ANTERIOR HORN CELLS OF CASE 1.  
Note preservation of Nissl substance. Eosin methylene blue.  $\times 160$ .

palely. Nucleoli sometimes could not be distinguished. In a fair number of nerve cells there was evidence of chromatolysis of varying degrees and there was a tendency for the tigroid material to concentrate around the periphery of the cytoplasm. Vacuoles were present in the cytoplasm of some of the anterior horn cells and these apparent spaces were surrounded by tigroid material which appeared to be normal (Fig. 5). These vacuoles were a prominent finding in one case especially in the lumbar region. In many of the neurones in which the nucleus was located centrally it composed the bulk of the cell. A few cells were noted in which only the outlined remained



contained inclusions of fat or were vacuolated (Fig 7) The vacuolation was striking in one case and was similar to that found in the



FIG. 6. NUMEROUS PHAGOCYTES IN THE VACUOLIZED NERVE NEAR ITS EMERGENCE FROM THE MEDULLA. CASE 2.  
Cresyl violet  $\times 800$

anterior horn cells of the spinal cord of this individual. With the Nissl stain the vacuoles appeared as clear unstained spaces surrounded by Nissl substance which was moderately well preserved

nucleus of the vagus stained diffusely and homogeneously so that the Nissl granules were well defined in only a few. There was a tendency to condensation of the Nissl substance about the periphery of these cells. The number of cells was slightly reduced in number especially in the dorsal motor nucleus and the nucleus ambiguus. Some of the nerve cells were shrunken and were surrounded by wide spaces. Nuclei were absent in some of the cells or they were found to be placed aberrantly. Some nerve cells of the brain stem, notably those of the nucleus of the tractus solitarius and dorsal motor nucleus of the vagus, were surrounded by satellite glial cells and neuronophagia was seen here and there. The nerve cells of the other nuclear masses of the medulla showed mild to moderate chromatolysis with homogeneously pale staining cytoplasm, shrinkage, and widened perineuronal spaces. There was congestion throughout. In one case, as previously noted in the description of the spinal cord, there were numerous discrete, small, perivascular hemorrhages throughout the brain stem, without any evidence of inflammatory reaction.

Many funiculi of the vagus and hypoglossal nerves, both in their intramedullary and extra-medullary portions were examined, in addition to several bundles of the accessory and glossopharyngeal nerves. The most striking changes were noted in the vagi and consisted of (1) marked edema, (2) swelling and fragmentation of the myelin sheaths, (3) increased neurilemma cells with many phagocytes and an occasional lymphocyte, (4) marked axonal degeneration, as evidenced by swelling, beading, fragmentation, "corkscrew" formation and dissolution of the axis cylinders, and (5) congestion. In addition it should be noted that in one case, the number of phagocytes in the vagus nerve was quite marked (Fig. 6). These phagocytes were not unlike the "foam" cells seen in polyomyelitis, in which disease however they are usually found in the spinal cord rather than the peripheral nervous system. A mitotic figure was seen in one sheath cell of the vagus nerve. The other medullary cranial nerves showed similar but less profound changes.

The pons and mid-brain revealed the same changes as enumerated above. The nuclear masses of the facial nerve were the most severely involved of the cell groups. The cells were shrunken, had wide perineuronal spaces and some were undergoing chromatolysis, and

composed the cellular bulk and nucleoli were absent or fragmented. The nucleus was not seen in some cells or it was eccentric. Not a few cells contained fatty pigment and small vacuoles. There was some satellitosis especially notable in the upper cortical layers and in some regions there was an increase in the number of glial nuclei in the first layer. The oligodendroglia of the white matter were swollen. The cerebral tissue was congested. In one case numerous discrete small focal perivascular hemorrhages were seen in both the white and gray matter. There was no perivascular infiltration of inflammatory cells. The meninges were slightly thickened and here and there a few lymphocytes and an occasional histiocyte were seen.

Perivascular cuffing with round cells was observed in the glomerular layer of an olfactory bulb in the single case in which they were examined microscopically. This is the only instance of perivascular cuffing seen in the central nervous systems of these cases.

**Cerebellum.** The cerebellum revealed changes similar to those in the cerebrum. Some of the Purkinje cells and the cells of the dentate nuclei demonstrated chromatolysis and shrinkage. There was a moderate decrease in the number of Purkinje cells. The cells of the granular layer were normal. There was a slight increase in the glial nuclei in the molecular layer. The white matter and blood vessels were essentially normal.

In general the pathological changes became progressively less severe as the neuraxis was examined in an ascending manner. The structures most affected in the nervous system of these individuals were the peripheral and cranial nerves. The changes in the central nervous system appeared mild in comparison and the majority of them would appear to be secondary to those in the peripheral nervous system. In other words many of the central nervous system changes were apparently of a readily reversible nature. The absence or rarity of neuronophagia in the brain and spinal cord and the relative degree of preservation of the Nissl substance was notable. With the exception of the spotty outfall of the neurones of the various gray structures of the spinal cord and nuclei of the brain stem the pathology was minimal. Nonetheless the histological changes in the central nervous system although comparatively mild were definite. To summarize the central changes there was (1) shrinkage, vacuolization

The cells of the various nuclei of the fifth nerve (mesencephalic, sensory, motor) and the abducens nuclei demonstrated some chromatolysis and shrinkage. The intra-pontine and extra-pontine portions of the abducens, trigeminal and acoustic nerves showed early degeneration. The involvement of the axones of the facial nerves was the same as that noted in the vagus.

Cerebral hemisphere.—Representative sections from various portions of the cortex of the frontal lobe, motor area, occipital lobe,

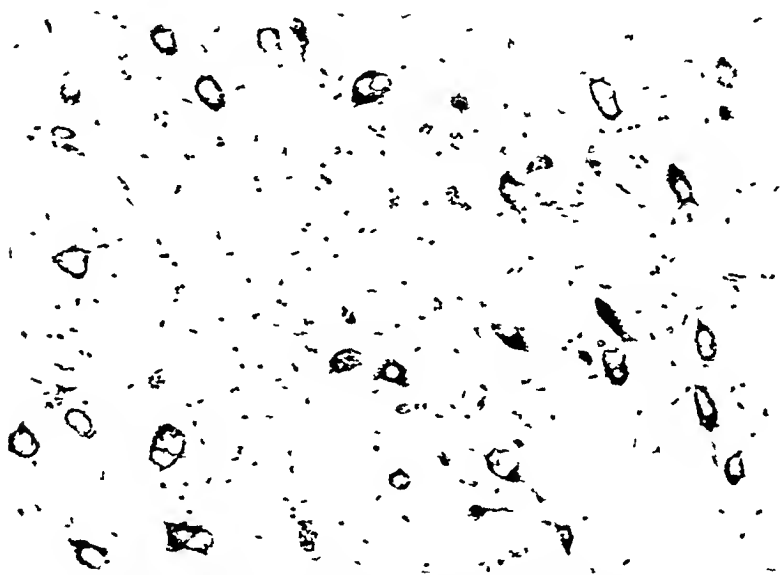


FIG. 7. THE FACIAL NUCLEI OF CASE 1 TO SHOW THE VACUOLIZATION OF THE NERVE CELLS AND THE RELATIVE NORMALITY OF THE NISSL SUBSTANCE.  
Cresyl violet  $\times 350$

Ammon's Horn and from the basal ganglia were studied. The abnormalities noted were (1) slight "outfall" of nerve cells (2) the nerve cells sometimes stained uniformly and palely and the nuclei were absent or eccentric (3) shrinkage of the ganglion cells with widened perineuronal spaces (4) congestion (5) swelling of the oligodendroglia of the white matter and (6) slight thickening and cellular infiltration of the meninges.

Some nerve cells of the cortex had lost Nissl substance, were shrunken and had widened perineuronal spaces. In some the nucleus

1. The purpose of this document is to provide a comprehensive overview of the current status of the project and to identify the key areas that require further attention. The information presented herein is based on the most recent data available and is intended for the use of management and other stakeholders.

2. The project has made significant progress since the last report, with several key milestones being achieved. However, there are still a number of challenges that need to be addressed in order to ensure the successful completion of the project.

3. The following table provides a summary of the project's progress to date, including the completion of tasks, the identification of risks, and the implementation of corrective actions.

4. It is important to note that the project is still in the early stages of development, and there is a need for continued monitoring and evaluation of the project's progress. The following table provides a summary of the project's progress to date, including the completion of tasks, the identification of risks, and the implementation of corrective actions.

PROJECT SUMMARY

5. The project has been successfully completed, and the results have been used to inform the development of the new system. The project has been a success, and the results have been used to inform the development of the new system. The project has been a success, and the results have been used to inform the development of the new system.

CONCLUSION

6. The project has been a success, and the results have been used to inform the development of the new system. The project has been a success, and the results have been used to inform the development of the new system. The project has been a success, and the results have been used to inform the development of the new system.

7. The project has been a success, and the results have been used to inform the development of the new system. The project has been a success, and the results have been used to inform the development of the new system. The project has been a success, and the results have been used to inform the development of the new system.

8. The project has been a success, and the results have been used to inform the development of the new system. The project has been a success, and the results have been used to inform the development of the new system. The project has been a success, and the results have been used to inform the development of the new system.

chromatolysis, and nuclear abnormalities in nerve cells of the spinal cord, brain stem, cerebrum, and cerebellum, (2) wavy and irregular axones and dendrites of the neurones of the spinal cord and brain stem, (3) the rare occurrence of a binucleated nerve cell in the lumbar cord, (4) the presence of small discrete foci of perivascular hemorrhage in the absence of other inflammatory reaction and the absorption of blood pigment by the anterior horn cells of the spinal cord (in one case). Finally, the presence of a marked degree of phagocytic reaction in the peripheral nervous system and its absence centrally, offered an unusual contrast.

#### VISCERAL PATHOLOGY

The examination of the viscera showed consistent changes in the three fatal cases. These changes have been described in detail elsewhere (Sabin and Aring, 1941), and will be summarized here. On gross examination there was acute passive congestion and toxic change especially in the liver, kidneys, heart, and spleen. There was some fatty infiltration in the liver especially notable about the central vein areas. Widespread softening had occurred in one adrenal gland in one case. The lungs showed varying degrees of atelectasis of the lower lobes with some slight compensatory emphysema. There was a patchy type of lobular pneumonia, undoubtedly secondary to aspiration, and an acute bronchitis in all cases.

On microscopic examination significant abnormalities were noted in the adrenal glands of the three cases. There were areas in which degeneration of the cortical cells had occurred and in which there was an accumulation of mononuclear cells. In one instance mononuclear cells were contained in great numbers in the perineurium of the adrenal nerves. In some places in the glands collections of lymphocytes and plasma cells were contained in structures which appeared to be dilated lymphatics, or in sites of degenerated cortical cells. In one case the only abnormal finding in the adrenals was focal vacuolization.

The heart in two cases contained diffuse interstitial infiltration with polymorphonuclear and mononuclear cells. In one case necrosis of scattered muscle fibers had occurred, and the remnants of the fibers were infiltrated by phagocytes. There was a focal inflammatory

infiltrate in the wall of a coronary vein in one case. This individual had also a focal phlebitis of a pulmonary vein, the reaction consisting of polymorphonuclear and mononuclear cells.

In the liver in all cases there were small accumulations of mononuclear, and occasional polymorphonuclear cells within the substance in the portal spaces and in the capsule. There had occurred also focal necrosis of liver cells with cellular infiltration and areas of focal fatty degeneration without much cellular infiltration.

In the kidneys collections of mononuclear cells were found in the interstitial tissue especially between the tubules. The tubules and glomeruli in these areas were intact.

The spleen contained an extreme abundance of red corpuscles and the presence of macrophages was noted. Malpighian bodies seemed reduced in number undoubtedly due to the excess of splenic pulp.

#### ANIMAL INOCULATION

Sabin and Aring have recorded the unsuccessful attempt to induce 'infectious polyneuritis' in mice, guinea-pigs, rabbits, and monkeys by inoculation with fresh sterile samples of the affected visceral and nervous organs. No one has yet succeeded in transferring the disease to animals since Bashford's report, nor in culturing an organism from affected tissues.

#### DISCUSSION

It is obvious that none of the titles advanced as names for the disease are satisfactory. There is at present little proof for our suspicion that the disease is infectious or infective. Infectious polyneuritis is usually not febrile. 'Ascending' used as a descriptive term to indicate the spread of the disease fails in its duty. The patients may not have facial diplegia or 'albumino-cytologic dissociation', although these terms are more nearly correct than most of those associated with this disease. Neuritis when analyzed has no different connotation than neuritis. Eponyms which by elimination would appear to be the most satisfactory under the circumstances have failed on analysis in this instance. Landry's name would have sufficed if the case described by Landry had not been disclosed to be most likely one of nutritional deficiency (Brown 1938). Guillain

and Barré have eliminated their names from consideration by their edict that all cases with the disease recover

The manifestations of "infectious polyneuritis" may be protean, although the condition is usually quickly recognized by anyone who previously has studied a case. A widespread flaccid weakness, following on an upper respiratory infection, should immediately arouse the suspicion of the physician that he is dealing with "infectious polyneuritis." The term "motoneuromitis," a favorite with some clinicians is titillating, but somewhat misleading. Sensory manifestations appear in these patients almost without exception even though flaccid paralysis is the more dramatic.

With the realization that the viscera are involved pathologically, one should look for abnormal clinical signs caused by these lesions. McIntyre (1937) has recorded the clinical signs of toxic changes in heart muscle similar to those found in diphtheria, in a patient with "infectious polyneuritis" who was studied clinically with the aid of an electrocardiograph.

The presence of a high protein content (with few or no white blood cells) in the cerebrospinal fluid is helpful in the diagnosis but may not be a requisite. Possibly this abnormality of the cerebrospinal fluid might be found always if several spinal punctures, spaced appropriately, were done.

It would be our thought that one should look elsewhere than in the nervous system for the causative agent. In most instances the visceral pathology has been neglected for that in the nervous system in "infectious polyneuritis." Involvement of the viscera (adrenal gland, liver, heart, kidney, and spleen) has been found in three instances, even though pathological studies of the viscera were not painstaking. The visceral changes resemble those seen in such diseases as diphtheria and typhoid fever, where a toxin elaborated by a micro-organism is usually held responsible. Sabin and Aring (1941) have noted that pathological changes of the viscera and of the nervous system in "infectious polyneuritis" are unlike those that would be expected from the effects of a pantropic virus. The possibility that a study might be fruitful on the organisms responsible for the respiratory infection which may precede the onset of "infectious polyneuritis" has been considered. It has been noted toward this end that a study of the



bacterial flora of the respiratory tract of these persons should be made, and that attempts should be made to reproduce the syndrome with toxins elaborated by these bacteria.

In the nervous system the primary site of damage appears to be in the peripheral nerves and ganglia. Neuronal changes in the central nervous system are widespread, but they are not apparently of such severity as to be irreversible. In fact most of the central changes appear to represent chiefly a reaction to injury of the peripheral nervous system.

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# THE CLINICAL EPIDEMIOLOGY OF POLIOMYELITIS<sup>1</sup>

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The title of this article deserves some explanation for the term *clinical epidemiology* is new, however old the activity it describes may be. Clinical epidemiology (1) may be described as what the doctor thinks about the circumstances under which a given disease appears. It is based more upon the exercise of clinical judgement than upon the use of statistics, or upon experiments in the laboratory from which analogies may be drawn for application in the human field. It is obviously only one of several forms of approach to the study of the ecology of disease, and is a supplement rather than a substitute for the statistical approach (2, 3). For, as the late Dr. Theobald Smith (4) has implied, both forms are necessary and should be used to tunnel into the mass of disease from two extremes. But in the case of poliomyelitis this emphasis on the clinical side is made advisedly, because during the last 20 years it has been evident that not only were we learning more about the disease in the monkey than in man, and more about figures than facts but we seemed to be satisfied with this form of endeavor.

*Historical* Historically the epidemiological aspect of poliomyelitis disease is not just a side light. It is closely associated with the whole story of the disease. For from the moment that acute paralysis of children became recognized, people have been deeply concerned with questions as to how and why this dread disease came about. There is hardly a comprehensive article which has ever been written on poliomyelitis in which the author did not become involved with questions of epidemiology. And so the history of the epidemiology of poliomyelitis is essentially the history of this disease (5).

To review this briefly, it may be recalled that although there are

<sup>1</sup> The John W. Wickoff Lectures for 1941, presented at New York University College of Medicine, February 4 and 5, 1941.

vague and short references about poliomyelitis which come down to us through many centuries, most medical historians are agreed that the first *clinical* description of poliomyelitis was not made until the end of the 18th century. It can be found in the writings of the English physician (or early pediatrician), Michael Underwood. Here a doubtful account appears in the first editions of his textbook on Diseases of Children, which was improved in later editions. It is a somewhat feeble effort to describe a new disease. Underwood was aware of the fact that paralysis occasionally occurred in young children following a bout of fever, and in order to make his textbook complete he added a description of this unusual malady. He believed it to be due to "teething or to foul bowels," and says that it occurred, "seldom in London than in other parts of this kingdom." Another good early description is that of Monteggia, and it came from Italy in the year 1829 (6). He believed he was dealing with a special kind of paralysis in children initiated by a special fever of two or three days duration. And so between these two descriptions a new disease was born.

After Monteggia, came Badam's report (7) containing the first reference to an epidemic. In it, four cases were accurately described in England. They occurred during the summer of 1835, in the small town of Worksop, which is in the midlands in England. Badam's paper prompted Heine (8), an orthopedist in Cannstadt, Germany, to report his own experience with a larger number of cases in a monograph published in 1840, and the disease was at last on firm ground. For Heine gave an excellent clinical analysis pointing out that the symptoms indicated an affection of the spinal cord.

But poliomyelitis was not destined to be quickly recognized as an important or common disease. A period of about forty or fifty years elapsed before its *significance* was generally appreciated and before much more was said about its epidemic form. We know that it was present in this country during that period, probably the first date which can be assigned is that of 1810 (9). We know this because in the 1830's there were certain orthopedic surgeons in both Philadelphia and Pittsburgh who were enthusiastic over Strohmeyer's tenotomy operation and in their operative reports on deformed limbs, they gave dates as to when some of their crippled patients got paralyzed. Apparently there was no great dearth of paralyzed children available for operation at that time.

We also know that a probable American epidemic occurred in Louisiana in 1841 which was described in a brief ten line report (10) But why the epidemic character of this disease received so little attention is a question which has puzzled many students of this disease It is easy to imagine that many epidemics must have occurred but passed unrecognized, and yet this explanation is not entirely satisfactory either In any event about the year 1880 the character of the disease seemed to change from that of sporadic to an epidemic disease From a curiosity the disease became a periodic scourge

The first appreciable epidemics were described in Sweden in the 1880's Then with ever increasing rapidity, reports appeared from many countries The first definite American epidemics were those reported from New England in the early 90's (11) The best known of these was discussed by Dr C S Caverly, (12) the president of the State Board of Health of Vermont, who made two local observations of fundamental importance First, he was struck with the fact that many of his cases in the epidemic of 1894, occurred in the Otter Creek Valley of Rutland County, Vermont (12, 13) This is among the earliest references to the association of the disease with water courses, and one which was reflected later in Sweden by the thesis which Kling developed into his "*theorie hydrique*" (14) It should interest us again today Secondly, Caverly is also credited as being the first to call attention to the variant clinical forms of poliomyelitis, to be described by Wickman later, as *abortive* poliomyelitis

During this period (1885 to 1905) most of the work on this disease was being done in Sweden The names we should remember are those of the pediatrician, Medin, and his pupil Wickman (15) Wickman devoted the best years of his life to the clinical epidemiology of poliomyelitis (15) The secret of his ability to study this aspect of the disease was based on the fact that he also recognized a characteristic train of symptoms, which might or might not end in paralysis Not only did he recognize the abortive case but he also recognized its significance to the epidemiologist, for by including them in his studies, he was able to trace the course of the disease in small villages in a manner that none before him and few since have succeeded in doing From his long series of investigations he concluded that the disease was contagious, and he developed a theory of human carriers But he also believed that it could be spread by means other than direct

contact, he believed that epidemics could be milk borne. His contributions were great and the important thing is, that he was concerned only with the spread of the disease in man, and not in monkeys. This was natural, because the virus was unknown and there was no experimental disease at that time.

A few years later in 1908, when Landsteiner and Popper (16) discovered the virus of poliomyelitis, there came a brief period of five years or more in which tremendous advances were made. In these, Dr. Flexner of this country took no small part, sharing with Lewis the discovery that the virus could be isolated from the nasopharynx of the monkey (17)—a finding which soon led Landsteiner, Levaditi and Pastia (18), and at about the same time Flexner and Clark (19), to find the virus in the throat of human cases. Too much of this period which antedated the first World War, has been forgotten in late years. It was a period when Thomsen in Copenhagen, (whose work is seldom mentioned today) discovered that you could infect monkeys by rubbing the virus on their nasopharynx (20), that you could infect them intraperitoneally with extremely small doses of the virus, and that different species of monkeys showed different degrees of susceptibility to infection (21). It was a period in which three Swedish investigators, Kling, Pettersson and Wernstedt (22), took advantage of the newly discovered methods on the isolation of the virus from the nasopharynx in living patients, and succeeded in bringing these new methods out of the experimental laboratory, and into the clinical laboratory. They were the first to find the virus in the stools of human cases. Using filtered washings from the throat and from the colon, they inoculated their human material into monkeys intraperitoneally and also into the sciatic nerve—and reported an amazing number of positive tests in isolating the virus from the nasopharynx and from stools of acutely paralyzed patients, abortive patients, and carriers. A better appreciation, however vague it may have been, of the *extra-neural* existence of the virus came into being as a result of this work. To them should go the credit for the first extensive, *clinical and laboratory* study of the epidemiology of poliomyelitis. There was, however, one unfortunate feature about these experiments, namely, that their criteria for determining the presence of the virus were not as definite as they should have been. Particularly was this true of the interpretations of the

lesions in the spinal cords of the inoculated monkeys. At least some of these lesions would not be accepted today, and so it is difficult to decide how many times they actually did find the virus. But although the experiments were not accepted in toto they marked the beginning of a new era in the history of poliomyelitis. With subsequent work in this country came the demonstration of the virus in the nasopharyngeal washings of a group of familial contacts by Flexner, Clark and Fraser in 1913 (23),—and a confirmation of this finding within the same year by Kling and Pettersson (24) in Sweden. This was the beginning of the experimental evidence to show that “healthy” carriers might exist among *family groups* where there had been a case of paralytic poliomyelitis. The best and last clinical epidemiological study from this period is that of Taylor and Amoss who found the virus in the nasopharyngeal washings from two children during a family epidemic (25). It was a pity that this type of clinical epidemiological investigation was not pursued further, but a number of features tended to shift the emphasis at that time into other directions.

The subsequent period (1917–1930) was one which was initiated by a need for the standardization of laboratory technique for those engaged in work on this disease. This need was great. Not only had some of the original results of Kling *et al* (22), been dependent upon “lesions” which not all laboratories would accept, but a series of other reports appeared (several of them from this country) in which the isolation of the virus was claimed under a variety of questionable circumstances, indeed the evidence presented in these reports would certainly not be accepted today. It seemed essential to define the diagnostic criteria for the identification of poliomyelitis virus, and to demand more rigid controls in experimental work of this type. The outcome was, that investigation of this type was taken out of the hands of clinicians and was returned to the experimental laboratory. It became a period of standardization not only of criteria but of methods—a period in which the experimental disease in the monkey was studied intensively and in one particular way. One strain usually the M V strain, one species of monkey, the rhesus, and one (or at most two) routes of inoculation, the intracerebral (or the intranasal) route, were the standard procedures to be followed. It was a period in which some of the concepts built up by clinical investigators of the

decade before, were broken down by the experimentalists. It was a period which culminated in the belief that poliomyelitis virus is strictly neurotropic in its capacity to invade the body of the monkey (26), or even man (27). It was also the period when the neutralizing activity of human sera set up against the M V (or the Ayrcock) strain was widely used as a method of epidemiological study (28). It was the period when statistical epidemiology seemed to take precedence over clinical and field epidemiology. No doubt it was a healthy stage in the history of the disease. It certainly left its mark on the present generation, for it is this aspect of the epidemiology of poliomyelitis (namely the experimental and statistical point of view) which is the one about which most reviews have been written. Because of this familiarity I will not try to go over this ground again.

Before proceeding with recent work it may be well to review some of the accepted principles which concern the distribution of poliomyelitis insofar as its geographical, seasonal and age incidence is concerned.

*Geographical distribution*—Poliomyelitis is world-wide in distribution and it has been said that no country, from which records are available, is known to be entirely free from sporadic cases (29). But in general it is a disease of temperate climates and both the endemic rate and the frequency and severity of epidemics increase with the distance from the equator. Scandinavia, Northern United States and Canada, Australia and New Zealand are the regions where the disease seems to be most common.

*Seasonal distribution* Clinical poliomyelitis is now recognized essentially as a disease of summer and fall, although sporadic cases and even epidemics may occur during any month of the year (30). It is unusual for epidemics to begin before the onset of warm weather and, while there are numerous exceptions, epidemics ordinarily disappear with the approach of cold weather. It is not in fact, an uncommon experience for an epidemic to start late in the summer, and apparently to cease with the coming of winter, only to reappear in the same area again on the following spring and to run its course through the entire subsequent summer.

*Rainfall* Opinions are conflicting as to whether poliomyelitis is more apt to occur during dry summers or wet summers but there is a



slight balance in favor of the former. In Sweden, Gard (34b) believes that during epidemic times, the attack rate goes up periodically within 6 to 10 days after rainfall and particularly heavy rainfall. He believes that both rainfall and temperature exert a decisive influence on the appearance of poliomyelitis. Somewhat similar, though less definite indications may be found in some of the reports from this country (35).

*Urban and rural distribution.* Clinical poliomyelitis also has predilections for certain types of surroundings within the same general area, for in spite of some disagreement (31) on this point the attack rates are apt to be higher and the disease more severe during epidemic times in the suburbs or outskirts of a city than in the most densely crowded areas (32, 33). In other words, according to several authorities not only is poliomyelitis a summer disease, but it is also a *rural* disease. The explanation of this feature has by no means been settled for one is free to choose as to whether the influence of season or place exert themselves more as features which tend to spread poliomyelitis virus, or more as features which tend to affect the resistance of the host.

To the author it seems logical (for reasons to be mentioned later in this review) that the rural prevalence of poliomyelitis, its summer prevalence, and its prevalence in temperate zones may be linked together in some mysterious way. The missing link or links probably represent environmental factors of considerable epidemiological importance. One can only conjecture what they are, but it is logical to suppose that some of these factors have to do with the dissemination of the virus.

*Host susceptibility.* No attempt will be made to review the extensive literature dealing with natural (hereditary) resistance to poliomyelitis. Most of this literature is concerned with the types of individuals who acquire *paralysis* rather than the types who acquire the commoner non-paralytic forms of the disease. Evidence has furthermore, been assembled to indicate that familial tendencies to acquire poliomyelitis exist (91), comparable to those seen in other infectious diseases such as, for instance, tuberculosis and rheumatic fever.

One acquired feature which seriously affects a child's resistance to the acquisition of poliomyelitis and to its ravages, is the *recent*

*removal of tonsils* It can be considered a practical fact that during the Toronto epidemic of 1937, among children between the ages of 3 and 12 years, acute poliomyelitis developed more often in those recently tonsillectomized than in others, and among the children with poliomyelitis, the incidence of the more severe (bulbar) form was more than twice as great in those whose tonsils had been removed as in the others (92). The mechanism of this artificial enhancement of susceptibility has not yet been established.

*Age incidence of poliomyelitis* Among all the mysterious and controversial features about poliomyelitis there is at least one upon which all are agreed, which is, that children are more susceptible to the paralytic form of the disease than are adults. In this respect poliomyelitis simulates such widespread and common diseases as diphtheria and measles, and it is assumed that the explanation for the age distribution is the same in all three diseases, namely that adults fail to contract the disease so readily because they have acquired immunity to it during childhood. But there is not so much agreement when it comes to an explanation of the exact method in which adults have acquired their immunity. To answer this question there have been many comparative studies on the age distribution of clinical cases of poliomyelitis under different epidemic conditions. As an early example one may quote the conclusions drawn from comparative studies on the age incidence of poliomyelitis by Frost, who in 1913 (36) pointed out that the age incidence varied with the concentration of the population. During the subsequent 20 years, others (37) presented evidence to substantiate this view, namely that the more densely populated the community, the younger was the age of those affected. This harks back to our recent mention of the severity of rural epidemics of poliomyelitis. This severity of rural poliomyelitis, with many adult cases and a high mortality, was originally interpreted as indicating that rural adults might be more *susceptible* to poliomyelitis than were urban adults. The theory postulated that in those communities where the opportunity for contact was high such as the city, there was an enhanced facility for the acquisition of *subclinical* and perhaps *non specific immunity*, whereas in those communities where the opportunity for contact was low, the children and young adults did not have the benefit of this type of immunity.

But whatever the explanation may have been of this contrast between the age incidence within urban and rural communities, it is more difficult to be dogmatic about the situation today, because the age incidence of poliomyelitis seems to have undergone certain fundamental changes within the past 20 years. These changes point to a general increase in the tendency of poliomyelitis to attack the higher age groups all around. Not only has this been noted in this country but in Sweden, and Australia as well (38). It is now apparent that the age incidence of urban cases in New York City in the epidemic of 1931, was almost identical with that which had been noted in rural New York State in 1916 (39). With this general, and modern shift in age incidence, the difference in age incidence between rural and urban populations often disappears, and in at least two recent epidemics in this country the findings of a decade or two ago have even been reversed, namely the rural cases have even been found to be younger than the urban cases\*. If one is to explain this according to the reasoning of a generation ago, one would have to assume that various populations in general, and urban populations in particular, are becoming *more susceptible* to poliomyelitis. On the other hand the increasing prevalence of poliomyelitis in the higher age groups might be due to other reasons. It might be partially due to a broadening of clinical diagnostic criteria and to the inclusion of a greater number of abortive types (for we know that abortive poliomyelitis is found in a slightly older age group than that of the paralytic cases) (40). Or it might be partially due to the fact that more poliomyelitis virus was reaching more people than was formerly the case, in other words, it might be a question of dissemination and dosage. We will have occasion to refer to this later.

*Neutralization tests* It seemed at one time as if many of these questions as to whether rural people were less immune to poliomyelitis, or whether people who lived in the tropics (where poliomyelitis was scarce) were less immune etc., could be answered by the use of the neutralization test in somewhat the same manner in which this test has been used for the study of the epidemiology of yellow fever. From the start there were technical difficulties about these tests with human

\* These two epidemics represent those of Michigan in 1939 and 1940, and of south western West Virginia for the same years.

sera which were originally set up with one strain of poliomyelitis virus and with small numbers of monkeys, instead of with several strains or with large numbers of mice as could be done with viruses readily infective for rodents. Furthermore, it was assumed at first that the presence in human serum, of substances which were capable of neutralizing a given strain (usually one of the standard monkey-passage strains) of poliomyelitis virus, could be interpreted as a *specific* finding which indicated that the person from whom the serum came was actually immune to poliomyelitis.<sup>3</sup> But it presently became apparent that those individuals who had had the paralytic form of poliomyelitis did not possess an excess of neutralizing power in their blood for in some comparative series, the convalescent patients even showed less of this property than could be found in the blood of normal individuals. It also became apparent that not all strains of poliomyelitis virus were alike. In fact the differences between some strains are so great that we might even be justified in regarding poliomyelitis as a group of diseases. (Indeed a situation not unlike that which exists in influenza may be present.) More recently Schaeffer and Muckenfuss (44) decided that from both a technical and clinical standpoint the test was inadequate, and Brodie, *et al* (45), and later Burnet (46) both decided that whether the technical procedures were adequate or not, the results had little to do with the immunity of the individual patient to poliomyelitis. Consequently we are apt to accept with some reservations those concepts<sup>4</sup> of the epidemiology of poliomyelitis which

<sup>3</sup> According to these crude tests it was found that the blood of new born infants possessed a certain amount of neutralizing activity to one of the standard strains of poliomyelitis virus, that this neutralizing property was either less or absent during early childhood, but that it increased gradually during adolescence until at about the age of 20 it was found that almost 80 per cent of those tested had some neutralizing power in their serum and this percentage was subsequently maintained during young adult life (28).

<sup>4</sup> Some of these concepts were concerned with the fact that man acquired immunity to poliomyelitis by a process of "immunologic maturation," or by "subclinical immunization," which simulated the situation which occurs in diphtheria. The findings indicated that the development of antibodies were almost more of a function of age, than of contraction of the disease. This was interpreted by some as indicating that the virus was round about us constantly, and that the process of immunization was going on steadily all the time. It was also less necessary under these circumstances to postulate that environment in the climatic and geographic sense had much to do with the actual spread of the disease. It emphasized (and rightly, no doubt) the importance of host susceptibility in determining the distribution of poliomyelitis. In some ways these concepts hark back

have been derived from the single strain (so-called standard strain) neutralization tests. This does not mean that all the possibilities of the neutralization test, as performed in monkeys, have been exhausted in this disease. Perhaps the use of more adequate technique particularly with the homologous epidemic strain (49), or the use of many strains may render it of much more value, or perhaps the discovery that some strains may be adapted to the cotton rat, and to mice, may be the basis of future studies in which an adequate number of animals can be used to make the results of this test statistically sound (47-48). But, so far, this test has not elucidated the problem as to how or when the majority of people acquire immunity to poliomyelitis.

So we must begin anew in our efforts to determine how man acquires poliomyelitis and in doing so it is always well to return to the patient, and start afresh from there. In this particular connection special attention will be placed on the abortive case. For it is likely that such cases represent the crux of many problems in the epidemiology of poliomyelitis. Their relative frequency during epidemic times is such that they may be of enormous immunizing importance to the juvenile population.<sup>5</sup>

*Abortive poliomyelitis.* Although it is unknown whether abortive cases of poliomyelitis are more frequent than they were twenty or more years ago at least they are recognized with more frequency in this country. This is due to the fact that the detection of the non-paralytic forms of this disease rests on firmer ground today than heretofore, because the virus of poliomyelitis has been repeatedly recovered from the nasopharynx (50, 52) and from the stools or intestinal washings (53, 54, 55, 56-58) in such cases.

Recognition of the existence of abortive poliomyelitis and measurements of the frequency of this form of poliomyelitis are of the greatest

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to the earlier views of Draper (41), who pointed out that there were indications of physiologic imbalance in persons attacked by poliomyelitis. They find expression in the views of Aycock (42), and Jungeblut (43), relating host susceptibility to poliomyelitis with endocrine activity or dysfunction. All of these views are more concerned with the importance of human susceptibility as it exists in poliomyelitis and other infectious diseases, than with the paths which may spread the virus.

<sup>5</sup> As a matter of fact it has been demonstrated with serial homologous strain neutralization tests that an increase in antibodies may occur in some patients who have sustained mild abortive cases of poliomyelitis (49).

assistance to the clinical epidemiologist in tracing the spread of the disease (40) For, instead of including only the occasional paralytic cases in his studies he can include in certain families (50, 58), institutions (55), or communities (57), almost all of the cases with clinical symptoms<sup>6</sup>

But the clinical diagnosis of abortive poliomyelitis is still difficult (51) and it is safe to say that for practical purposes, abortive poliomyelitis can only be diagnosed during an epidemic of poliomyelitis (59) Under these circumstances such cases are often found in small familial groups, that is, contemporaneously with the development of a paralytic case in one member of a family there may be an outburst of brief, febrile illnesses among the brothers and sisters of the paralyzed child From reports of more than 200 such cases observed in two epidemics in Eastern sections of the United States, abortive poliomyelitis can be described as an acute illness characterized mainly by symptoms which are the same as those often seen in the early stages of a case of paralytic poliomyelitis These include fever, lasting from 12 to 72 hours and generally accompanied by headache, vomiting, sore throat, occasionally diarrhea, occasionally pain in the back and limbs, and occasionally a stiff neck Such patients may frequently exhibit a slight degree of stiffness of the spine, if this sign (the spine sign) is diligently tested The brief illness is then followed by a period of malaise which may last a week or more Spinal fluid examinations made during, or just after the febrile period generally fail to reveal positive findings, such as pleocytosis and an increased globulin content, but this failure to find spinal fluid changes is not accepted as evidence that the lesions of abortive poliomyelitis, slight though they may be, are necessarily all extra-neural in location

It is obvious that the majority of these ill-defined (abortive) cases have often gone, and still go undefined and unrecognized under such designations as "acute gastro-enteritis," or "grippe" The practicing physician may hold his opinion about them in reserve, placing such cases in the category of suspicious poliomyelitis cases, but the epidemiologist must regard them with particular care

<sup>6</sup> Not all observers are agreed on this point Gard in Sweden (34a) believes that most of these *minor illnesses* which so often accompany an epidemic of poliomyelitis are examples of another infection which perhaps *facilitates* the entrance of the poliomyelitis virus into the host

There have been recent attempts in this country to determine how they compare in frequency to the paralytic cases (40). This ratio may well differ in different epidemics but unfortunately the diagnostic criteria may differ also. Leake (61) has pointed out that, in our large 1916 epidemic and preceding it, all but a few reported cases were paralytic in 1936—about 50 per cent, and in Virginia in the same year—about 14 per cent. In two epidemics (Connecticut—1931 and Pennsylvania—1932) in which an intensive study was made of this point, the mild cases (abortive and suspected abortive) were found to outnumber the paralytic cases by at least eight times (40). Consequently, if all the cases abortive and paralytic had been included in the official returns from these epidemics, the attack rates for poliomyelitis would have been found to be very different from those usually accepted. In fact, they would have approached the attack rates of highly contagious diseases. It comes down therefore to the fact that during epidemic times, poliomyelitis actually *is a common disease*, and its ability to give rise to widespread immunity should also be viewed in this light.

One of the first features that becomes evident in this connection is a refutation of the old statement (found in many textbook articles on poliomyelitis) that the disease seldom attacks more than one member of a family. What the textbook authors implied was, that the disease seldom *paralyzes* more than one member of a family, for multiple cases within families are frequent, and family epidemics are frequent and often explosive in character (34, 62, 50-57). The explosiveness of the family epidemic is a point which is brought out in sharp relief by paying close attention to the abortive case. The situation would seem to indicate that most of these families become infected through a common source—a feature reminiscent of the old question as to whether milk-borne epidemics of this disease may not exist. In any event, it becomes apparent that the disease seldom runs through a family as does measles with primary, secondary or even tertiary cases separated by an interval equal to the incubation period of the disease (62, 63). Institutional epidemics may also be of this same type (55). By the accumulation of more data about family and institutional outbreaks, supplemented with tests for the virus we should gradually learn more about the spread and circumstances under which the virus is distributed among groups of people of different ages and the expected

ratio of both healthy and convalescent carriers. A finding which has already come to light is that children under 5 are more apt to harbor the virus in their intestinal tracts during epidemics than are individuals above this age (56, 64).

### *Portal of entry*

From the epidemiologist's standpoint, the portal of entry is mainly important insofar as knowledge of the route whereby the virus enters the human body may give us a clue as to what the vehicle is which carries poliomyelitis virus to its potential victim. In other words, it is important if it tells us whether the virus is associated in nature with a droplet of nose spray, with contaminated food or water, or with a contaminated insect.

*Nasal mucosa* In 1935 the nasopharynx was accepted, almost universally in this country, as the portal of entry in poliomyelitis. In its favor was the fact that the virus had occasionally been detected in the human nasopharynx (52). Furthermore, it had been found easier to infect rhesus monkeys by instilling the virus into their nostrils, than to infect them by certain other routes. Particularly was this true of the experimentalist who worked with some of the highly virulent, so-called *standard* strains of the virus. But the significance of this ability to infect rhesus monkeys intranasally began to lose some of its force when it became apparent that an increasing number of neurotropic viruses are also infective if instilled into the nares of experimental animals. For instance, this can be accomplished with yellow fever virus in mice, and occasionally with rabies virus,—although it is obvious that such laboratory manoeuvres do not tell us much about the manner in which yellow fever or rabies spreads in man. Next, Sabin and Olitsky (65) pointed out that lesions may be regularly produced in the olfactory bulbs of the monkey when the virus was instilled *intranasally*, although they were not produced when the virus was injected *intracerebrally*. Thus it immediately became important to know whether these olfactory bulb lesions could be found in fatal human cases. There is still not as much definite information on this point as one would like but all the reports indicate that human olfactory bulb lesions do not occur with any degree of frequency in this disease. Landon and Smith (66) found very little pathological change



in 56 olfactory bulbs from their series of fatal human cases. Harmon and Levine (67) found only slight lesions in the olfactory bulbs in 2 out of 9 cases, and Sabin (68) reports that only with rare exceptions have significant changes been encountered in his series of human olfactory bulbs. These findings indicate that it is unlikely that the nasal mucosa and olfactory tract is an important portal of entry in man.

*Gastro-intestinal tract.* One American investigator, Toomey of Cleveland, has long been a champion of this route. His experimental evidence has been based on observations which seem to have indicated that infection of the central nervous system by the virus of poliomyelitis (which had been introduced into the gastro-intestinal tract) was facilitated by injury of the gut or by the supplementary action of the toxins of certain enteric bacteria (69). But prior to Toomey's work on monkeys, experiments were carried on in Europe by Kling, Levaditi and others (70, 71), and by Saddington in this country (72), who pointed out that it was unnecessary to devise complicated experiments in order to infect monkeys by the gastro-intestinal route, provided one used the proper species of monkey: for if one used the Java monkey (*Macacus cynomolgus*) instead of the rhesus (*Macacus rhesus* or *mulatta*) it was possible to infect the former by feeding the virus. Since then these results have been amplified (73, 74), and also the green African monkey (*Cercopithecus aethiops sabaeus*) (75) has proved susceptible to infection after feeding. And Howe has extended this work to the higher apes or chimpanzees (76). In some of his chimpanzees the olfactory tracts were cut prior to feeding (in order to preclude the entrance of the virus by that route) and yet infection was successfully produced. Whether the virus penetrated the mucosa of the mouth, the esophagus, the stomach or the small or large intestine has not been settled, but it is unnecessary to incriminate the olfactory bulbs in most of the feeding experiments. It would seem quite definite therefore that the disease can be produced experimentally by feeding the proper animal with the virus. This may or may not be of great significance for we have already warned against the danger of explaining the human disease in terms of experiments upon monkeys, but we should mention that, if one assumes that man cannot acquire poliomyelitis by swallowing the virus then we must assume that, in

this respect, man resembles the rhesus monkey more closely than he does the Java monkey, or the green African monkey, or the chimpanzee

*Cutaneous route* The importance of this route would be of major significance if it became necessary to hypothecate that the disease was spread by a biting insect. All one can say is, that it is easy to infect monkeys by injecting some strains of the virus under or into the skin and difficult to infect them with other strains (77, 78, 79). But it also should be remembered that poliomyelitis has been actually produced in man by this route (80). This was done accidentally of course at a time when vaccines were being tried in this disease.

Our knowledge of the various portals of entry in man can therefore be summarized with the statement that it now seems unlikely that the olfactory bulbs represent the usual portal in this disease. The oral cavity, and the gastro-intestinal tract seem more likely, the cutaneous route is a possibility.

#### *Portal of exit*

*Nasopharynx* From the time when poliomyelitis was first successfully isolated from the throat in man theories of the spread of this disease began to revolve about this region and have continued to do so for a generation. During this period the nasopharynx was more or less tacitly accepted both as a portal of entrance and as a portal of exit of the virus in man. According to estimates made in 1938 the virus of poliomyelitis had been isolated from the nasopharynx 29 times out of 287 trials (52). These results indicated that the optimum time for detecting the virus is in the first few days of the disease and they also suggested that about 6 per cent of patients seem to harbor the virus in the throat for fairly long periods of time. Owing to technical difficulties it is probable that this figure is not very accurate and probably too high for great liberality has been used in the interpretation of the earlier "positive" tests, gleaned from the literature. (It may be stated that in 76 tests performed in our own laboratory since 1931, we have never succeeded in isolating the virus from the nasopharynx after the fifth day of the disease.) It is quite likely nevertheless, that this presence of the virus in the throat is of epidemiological significance, although the part that oral secretions may

play in transmitting the virus from one individual to another is unknown. By the same token, however, it would seem today as if this nasopharyngeal location of the virus was of less significance than its intestinal location, for it is so much easier to find the virus in the intestinal tract than in the nasopharynx during convalescence.

*Gastro-intestinal tract* Since 1912 (22) there have been indications that the virus could be isolated from the intestinal tract. The main reason, however, that the intestinal work was discounted was that the diagnostic criteria used in the first experiments were not those which are generally accepted either then or now. A revival of interest in the intestinal tract came in 1937 when Harmon made brief mention of his experiments with 20 convalescent patients (81). He was unable to recover the virus from the nasopharynx but was successful with colonic washings from 4 of these patients. Since that time these findings have been repeatedly confirmed and it has now become apparent that it is at least twice as easy to isolate the virus from the stool as it is from the nasopharynx,—a fact, by the way, of which Kling in Sweden has been aware since 1929 (14). So within the last few years the idea that poliomyelitis may be an "intestinal disease" after all, has come sharply to the fore. The reason that it is easier to isolate the virus from the stools is, that it remains in the intestinal tract for longer periods of time. It has been repeatedly found there in the second or third weeks of convalescence. And within this period convalescent carriers have been demonstrated in from about 16 to almost 70 per cent of the cases tested (83). Occasionally the virus may persist in the stool for months as noted in the report of Lépine *et al* (54) who isolated the virus from a child which had sustained an abortive attack of the disease 125 days prior to the time when the test was made. This finding indicates the importance of determining the frequency with which convalescent carrier states occur, as well as their usual duration. It is a problem of first importance, for although it may be unknown whether the presence of the virus in the stools of patients is a direct or even an indirect link in the chain which actually leads this agent from one patient to another it is valuable to know when the virus is there. We need more knowledge about the presence not only of poliomyelitis virus but of other viruses in human stools for the idea that any virus disease might be spread by feces is

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relatively new to medical science.<sup>7</sup> We know nothing of the human epidemiology of such hypothetical diseases. In poliomyelitis it seems certain that during epidemic times and within epidemic areas, the intestinal carrier rate must indeed be high when one realizes the relative frequency of abortive cases and the number of these which may "excrete" virus in their intestinal tract during the first few weeks of convalescence. There are also several recent examples of true *healthy* intestinal carriers (55). All of them were under the age of 4 years and it is of interest and probable importance that it is in very young children that the carrier rate is highest (55, 56, 64). We soon find furthermore, that a distinction between a healthy and a convalescent carrier is not an easy one to make in this disease, for the symptoms of the abortive attack may be so slight as to escape recognition. But inasmuch as in the majority of the convalescent abortive cases the disease is not diagnosed, most of these convalescent carriers would come under the category of "healthy carriers" as far as the community is concerned.

Another question in this connection is: What is the virus of poliomyelitis doing in the intestinal tract (or the pharynx)? Is it growing there free in the lumen or in the intestinal lymphoid tissue, or is it excreted into the mouth or intestinal tract in the same manner as rabies virus appears to be excreted into the saliva? If the first suggestion is true, it rather refutes the idea that the virus is as strictly neurotropic in its affinities, as was once believed. There may indeed be some evidence to support a "viscerotropic conception" in view of Kling's findings of the virus in mesenteric lymph glands (84). The suggestion that the virus is originally excreted into the oral cavity, and eventually makes its way into the intestines because it is swallowed, also does not find much support, for it can be demonstrated in the intestines over longer periods than in the nasopharynx. Sabin's valuable experiments on both autopsy material and clinical cases suggest that virus may be absent in the nasopharynx while present in the intestinal tract (64). One must confess, therefore, that there is no good explanation to

<sup>7</sup> The only other pathogenic virus to date which has been isolated from human stools is that of foot and mouth disease (82). In unpublished experiments from our laboratory, suggestive results indicate that other viruses may occasionally exist, but adequate methods for their demonstration or identification have not been used.

account for the presence of the virus in the intestinal tract, but from an epidemiological standpoint it seems like a dangerous place for a pathogenic virus to be. Particularly is this true when one considers how much virus may be present in a single human stool (for somewhere between 1000 and 10,000 doses infective for the monkey are demonstrable in a 50 gram stool). It is easily seen then how great a quantity of virus must enter sewage during epidemic times and it becomes important to know something of the conditions under which it can be demonstrated here. Emphasis should be laid upon the point that, in spite of Kling's *theorie hydrique* (14), poliomyelitis does not appear to be essentially a water borne disease. The manner in which it usually spreads through the community is probably complex and not limited to a single route but it is worth calling attention to the fact that in small epidemics, cases have been grouped about rivers and streams which have been heavily polluted with sewage. We have had occasion to observe such a selective localization of cases about the polluted Naugatuck River in southwestern Connecticut on two successive years (57). The question then as to whether poliomyelitis may be demonstrated in sewage or polluted water becomes one of more than academic significance.

Before describing the experiences with sewage it may be worth mentioning the fact that poliomyelitis virus is quite stable, it survives well in 15 per cent ether and in low dilutions of phenol. In suspensions of human feces it keeps in the icebox for months. It is small wonder therefore that a virus which is stable and which gains access to sewage in such large quantities can probably be demonstrated there. To date there are 6 examples in which the virus of poliomyelitis has been successfully isolated from sewage, all of them during epidemic times. These include one from Charleston, S. C. (57) three from a hospital sewer in Detroit (57) one from New York City (85), and one from Stockholm, Sweden (86). From these tests we have learned that large quantities of the virus may be present in sewage during epidemic times and that the virus may be *transported* by sewage. Most of the positive results have been obtained in the vicinity of hospitals but this has not always been true.

The question has been raised, of course as to whether or not poliomyelitis virus may not be a normal inhabitant of sewage, like tetanus

bacilli, or tubercle bacilli. For the mere finding of these organisms in sewage would tell us little about the epidemiology of the human infections which these bacteria cause. And so of particular interest in this connection has been an experiment made during inter-epidemic periods to determine whether or not poliomyelitis virus may be present all the time—that is winter and summer, in good years and bad. If it were present at all times such a finding would be in keeping with Aycock's theory of the pathogenesis of this disease, namely that we are constantly exposed to the virus winter and summer, year in year out, and only when profound alterations occur in the host does the clinical disease come to the surface. To answer this question we have recently made a series of tests on sewage both in winter and summer. The samples tested represented both hospital sewers and main sewers from the City of New Haven, and one of the larger collecting sewers from New York City. From all these tests which have been carried on monthly for a year (1940-1941) a single positive result was obtained from New York City in September, 1940. This was not however the year of a large epidemic in New York City, but the virus was found in the local sewer during the month when cases of poliomyelitis had reached a peak for the year in that city. Limited as these findings may be they indicate that poliomyelitis virus is not as readily demonstrable in sewage during inter-epidemic times as in epidemic times.

And finally I wish to bring up again the fact that rural surroundings and summer weather are features which seem to be important in the spread of this infection. One cannot leave this aspect of the subject without recalling that within the last few years two or three other summer virus diseases, which also involve the central nervous system have been recognized, and their similarity to poliomyelitis is considerable. The first of these is St. Louis encephalitis. Its manner of spread is unknown but recently theories have been proposed which have to do with both sewage and mosquitoes (87). Another summer disease of the central nervous system is Japanese B encephalitis which is said to be mosquito borne. A third is equine encephalomyelitis, a mosquito borne disease of horses (or perhaps of fowls) which was epidemic in humans in New England during the summer of 1938 (88). Its geographical distribution among horses in some localities is said to be similar to that of poliomyelitis (89). It is likely that as knowl-



edge accumulates about these various summer encephalitides we may also learn something new about poliomyelitis

And so we are again brought to a consideration of poliomyelitis as a possible insect-borne disease, or at least to a consideration of an extra-human reservoir or of vectors in this disease. It is well known that relatively few animals have been shown to be susceptible to experimental infection by the virus of poliomyelitis, but the recent experiments which deal with infection of the cotton rat and other rodents have reopened the whole question of the possible existence of an animal reservoir. At least, however the virus has never been isolated in nature from any of the common animals birds or insects which have been tested during epidemics. In the literature of 25 years ago (90) the stable fly (*Stomoxys calcitrans*) was suspected of carrying the virus, on the basis of somewhat unusual experiments but definite proof of this was and still is lacking. Similarly the bed bug and house fly have been occasionally shown to be capable of mechanically transferring the virus but it is questionable whether we are able to interpret the clinical significance of these experiments. Several attempts have also been made to incriminate mosquitoes as vectors but all the published reports have been negative.<sup>s</sup> One difficulty in fitting the epidemiological facts as we know them to a biting insect, such as the mosquito, is that we do not have a situation similar to that which exists in malaria or yellow fever in which the infectious agent exists temporarily in human blood, as if it were ready during this period to be taken up by the mosquito. This does not eliminate the fact however, that a vector might not acquire the virus from another source (such as sewage for instance) and that subsequently this hypothetical vector could easily infect human beings by contaminating food or penetrating the skin.

In conclusion then, we do find certain features both seasonal and geographical which may indicate that a hypothetical extra-human host, vector or vehicle may exist in poliomyelitis as the latter does for instance, in cases of typhoid fever spread by the eating of con-

<sup>s</sup> Unpublished experiments in the author's laboratory have shown that the ingested virus of poliomyelitis (SK strain) can survive within (*Aedes aegypti*) mosquitoes for a period of at least two hours. We have been unsuccessful in carrying out satisfactory experiments to determine the ultimate time which this strain of virus can survive in this particular species.

taminated shell fish, or in dysentery in the case of contaminated milk or flies. In poliomyelitis there is ample opportunity for many extra-human agencies to come in contact with the virus during epidemic times, considering the enormous quantities of this virus which are occasionally found in sewage. I do not have to add that no such living vector has been demonstrated in nature, but an adequate search has not yet been made. One hardly needs to be reminded of the similarity of the discussions which took place over the epidemiology of typhoid fever or of yellow fever in past years. About 100 years ago arguments were frequent and bitter as to whether or not these last two diseases were contagious. In both of them strong extra-human factors were eventually discovered which were important in their spread and it was obviously a missing link (the unknown extra-human factor) which was responsible for the original differences in opinion about contagiousness. Consequently one can at least say that *historically*, the case for an extra-human host or vehicle in poliomyelitis is good, although there is no indication as yet, whether this host or vehicle is either animal, vegetable, or mineral.

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